

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Title page

Title: Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study

Author names and institutional affiliation(s):

Francisco de Assis Acurcio^{a,b,c}, Augusto Afonso Guerra Junior^{a,b}, Michael Ruberson Ribeiro da Silva^{a,b}, Ramon Gonçalves Pereira^{a,b}, Brian Godman^{d,e,f}, Marion Bennie^d, Hacene Nedjar^g, Elham Rahme^{g,h}.

^a Department of Social Pharmacy, School of Pharmacy, Federal University of Minas Gerais (UFMG), Belo Horizonte, Minas Gerais, Brazil;

^b SUS Collaborating Centre for Technology Assessment and Excellence in Health (CCATES), School of Pharmacy, Federal University of Minas Gerais, Brazil

^c Post-graduated Program of Public Health, Department of Social and Preventive Medicine, School of Medicine, Federal University of Minas Gerais, Minas Gerais, Brazil

^d Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK;

^e Division of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden;

^f Health Economics Centre, Liverpool University Management School, Liverpool, UK

^g Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

^h Department of Medicine, Division of Clinical Epidemiology, McGill University, Montreal, Quebec, Canada

Address for correspondence:

Francisco de Assis Acurcio [corresponding author]

Departamento de Farmácia Social, Faculdade de Farmácia, Universidade Federal de Minas Gerais. Rua Prof. Moacir Gomes de Freitas, 155 - sala 1048 B2, Belo Horizonte, MG, Brazil. CEP 31270-901

Phone: (+5531) 34096855 Fax: (+5531) 34096852

E-mail address: fracurcio@gmail.com

(Accepted for publication – Current Medical Research and Opinion)

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Abstract

Objective. To evaluate persistence on conventional DMARDs (cDMARDs) and anti-TNF therapies, and to identify potential determinants of discontinuation among individuals with ankylosing spondylitis(AS) living in Brazil and Quebec, Canada.

Methods. We conducted a cohort study of AS patients using health administrative data (2010-2015). One-year and 2-year persistence rates were assessed. Cox regression was used to identify potential determinants of therapy discontinuation.

Results. One-year persistence was less likely in Brazil for both anti-TNF and cDMARDs (Brazil: 62.1% and 30.7%, Quebec: 66.9% and 67.0%). The 2-year persistence rates were lower for both anti-TNF and cDMARD, but remained higher in Quebec (Brazil: 47.9% and 18.1%, Quebec: 51.5% and 53.5%). In multivariate Cox regression analysis, age, sex and comorbidities were associated with persistence in both countries. In Quebec, persistence did not differ between rural and urban regions or with socioeconomic status. While in Brazil, patients in regions with higher Human Development Index and those in cities with lower Gini index were less likely to discontinue therapy.

Conclusions. Canadian AS patients were more likely to persist on therapy compared to Brazilian patients, although rates were lower at 2 years in both countries. Socioeconomic disparity in persistence was found in Brazil, but not in Quebec.

Keywords. ankylosing spondylitis; anti-TNF agents; conventional DMARDs; medication persistence, cohort

Short Title: Persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that damages the spine by causing structural changes, including bone growth and fusion. Stiffness and functional limitation of the axial skeleton increase the risk of disability and reduce the quality of life of patients with AS [1-4]. AS patients may also develop arthritis in their peripheral joints [2,5]. AS prevalence ranges from 0.02% in Sub-Saharan Africa to 0.90% in Canada [5,6]. AS prevalence has not been determined in the Brazilian population to date; however, in Latin America AS prevalence rates range from 0.19% to 0.30% [7]. AS most commonly manifests in males in the second to third decade of life [3,8], and is associated with substantial economic burden to healthcare systems. Patients with AS added an extra €2475/patient to healthcare costs in Germany in 2013 compared with the general population, with key cost drivers being hospitalization and medicines, in particular anti-tumor necrosis factor (anti-TNF) agents [9,10]. Anti-TNF costs were also high among Brazilian patients with AS, with a median per patient monthly cost of US\$1650 versus (vs.) US\$25 for patients using conventional (non-biologic) disease-modifying antirheumatic drugs (cDMARDs) [11]. Indirect AS-related costs have also been substantial worldwide [12].

Anti-TNF agents use has greatly improved the AS treatment [8,13], with anti-TNFs are now routinely recommended by clinical practice guidelines for AS patients with persistently high disease activity following first line therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) [14]. cDMARDs may also be considered in AS patients with peripheral arthritis [14]. Appreciably improved health gain coupled with a similar safety profile in terms of infection and cancer risks have been demonstrated in AS patients

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

prescribed an anti-TNF agent compared with control (placebo) treatments [10,15]. These findings are similar to those reported in patients with rheumatoid arthritis and psoriasis, and are encouraging, given initial safety concerns with these biological medicines [16].

For optimal benefit, patient adherence to and persistence on prescribed treatment regimens are required. Persistence on treatment is considered an indication of its effectiveness, safety, and tolerability. Poor patient adherence and persistence to a treatment regimen may result in treatment failure and disease progression [17,18]. Suboptimal anti-TNF adherence and persistence have been frequently reported in real world settings [18,19], which is a concern.

Consequently, we performed a comparative analysis to evaluate persistence on cDMARDs and anti-TNF therapies, and to identify potential determinants of discontinuation among individuals with AS living in Brazil and Quebec, Canada, between 2010 and 2015. These countries were chosen as they both provide public coverage for cDMARDs and anti-TNF agents in AS, although with different reimbursement policies. This avoids issues of affordability which could affect anti-TNF utilization as observed in central and eastern European countries [20].

Patients and methods

Two cohorts of AS patients aged ≥ 20 years were constructed, one in Brazil and the other in Quebec, Canada using similar selection criteria to the extent permitted by the available data.

Patient Selection

Brazilian data

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

A national population-based cohort of AS patients was constructed using the High-Complexity Procedure Authorization database from January 2010 to December 2015 (the study period). Mortality and hospitalization records were obtained for these patients from the Mortality Information System and the Hospital Information System, respectively [21]. Within the Brazilian health care system, *Sistema Único de Saúde*, SUS, the anti-TNFs infliximab, etanercept, adalimumab and the cDMARDs, sulfasalazine and methotrexate, are provided free of charge to AS patients who meet the criteria of the nationally agreed protocols. Otherwise, there is 100% co-payment.

AS patients were identified from SUS data according to the international classification of disease (ICD)-10th revision codes M45.x, reported as the indication for prescribing the drugs of interest. To be considered as an AS case, patients were required to have at least 2 records of medicines dispensed for any of the specified anti-TNFs and cDMARDs associated with a diagnosis of AS in the study period.

Quebec data

Physician and prescription drug claims, hospital and demographic records from January 1997 to December 2015 obtained from the provincial health services administrative databases administered by the Régie de l'assurance maladie du Québec (RAMQ) were used. The databases are linkable by a unique patient identifier.

Individuals who had a diagnosis of AS between January 1998 and December 2015 were identified at the first diagnosis date. AS diagnosis was defined by 2 outpatient ICD-9 codes for AS (720.0) at least 30 days apart and within 2 years of each other or one hospital diagnosis (ICD-9 code 720.0 before April 2006 and ICD-10 codes M45.x on or after April 2006). AS patients who received at least one dispensed prescription for either a cDMARD

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

(hydroxychloroquine, methotrexate, sulfasalazine, leflunomide) or anti-TNF (infliximab, etanercept, adalimumab, certolizumab and golimumab) in the study period (2010-2015) and had a full year of prior drug coverage were eligible.

Cohorts definitions

New anti-TNF and conventional DMARD users

AS Patients from either Quebec or Brazil who had one or two anti-TNF prescriptions, respectively (with or without cDMARDs concurrently), were identified at the dispensing date of the first anti-TNF prescription (cohort entry date), [anti-TNF (+/- cDMARD) group, hereon called anti-TNF group]. In Quebec, the remaining patients formed the cDMARD group (hereon called cDMARD group). Selection criteria for the cDMARD group differed slightly in the Brazilian cohort. Because cDMARD use is much lower than anti-TNF use in the Brazilian database, the cDMARD group in the Brazilian cohort included those who used cDMARDs, but no Anti-TNFs during 1 full year or 2 full years of follow-up (for the 2-year analysis). Patients in the cDMARD group in both the Brazilian and Quebec cohorts were selected at the dispensing date of the first cDMARD prescription (cohort entry date). We adopted a new user design, where patients who used anti-TNF during the year prior to the cohort entry date were excluded from both the anti-TNF and cDMARD groups and patients who used cDMARDs during that year were excluded from the cDMARD group.

Follow-up

Study patients were followed from the cohort entry date until the earliest date of the first hospitalization lasting more than 60 days, death, or the end of the study period (December

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

31, 2015). In addition, for the Quebec cohort, follow-up ended at the end of the continuous coverage by the drug plan, when relevant, defined as a gap of > 60 days in drug coverage

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Exposure and outcome definition

Patients were considered exposed to their group drug (anti-TNF or cDMARD only) for the number of days supplied for the medicine plus a grace period of 60 days (drug-free interval).

Discontinuation of cDMARD therapy was defined as a gap of more than 60 days with no cDMARD supply. In case of failure of initial cDMARD monotherapy, patients can switch to another cDMARD or use a combination of 2 or more cDMARDs. cDMARDs were analyzed as a single class and starting another cDMARD while having a supply for the first cDMARD was not considered a therapy discontinuation. While, for the anti-TNF group, starting another anti-TNF while having a supply for a first anti-TNF was considered a therapy discontinuation since concomitant use of two anti-TNF agents is unlikely.

We described medication persistence at 1 and 2 years after cohort entry.

Patient baseline characteristics

The patient characteristics assessed at the cohort entry date included age, sex, region of residence, comorbidity scores and the number of in-hospital days due to any cause during the previous 2 years (general patient frailty) [22].

Comorbidity scores were calculated based on the Charlson Comorbidity Index (CCI) [23], using medical services data from 3 years prior to the cohort entry.

In addition, corticosteroid, NSAID and opioid use in the prior year were assessed in the Quebec cohort; these data were not available in the Brazilian database.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Socioeconomic status (SES) was also examined in both cohorts. In the Brazilian cohort, SES was assessed using the Gini index of per capita income by municipality of residence [24]. The Gini index ranges from 0 (no inequality) to 1 (maximum inequality). In the Quebec cohort, an SES index was available from RAMQ with subindices of social and material deprivation. This index was developed by the Institut national de santé publique on the basis of census data on neighborhood education level, employment/population ratio, and average income [25].

Statistical analyses

Descriptive statistics were used to report patient baseline characteristics in the two cohorts. The proportion of patients with a 1-year medication persistence was calculated by dividing the number of patients who did not discontinue the medication in the first year by the number of patients who had a full year of follow-up or more. The 2-year medication persistence was calculated similarly.

Mean and proportion differences with 95% confidence intervals (CI) were used to compare unadjusted outcomes between treatment groups within each cohort, respectively. Kaplan-Meier survival curves were plotted, and log-rank tests were performed to compare medication persistence between study groups. Multivariable Cox proportional hazards models were used to identify potential determinants of therapy discontinuation at 1 and 2 years, in the anti-TNF and cDMARD groups, respectively. Adjusted hazard ratios (HR) and 95% CIs were calculated. Potential determinants considered in the Cox models included age, sex, region of residence, SES, comorbidity score, general frailty, and calendar period of cohort entry (≤ 2012 or > 2012).

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

In sensitivity analyses, we allowed a drug-free interval of up to 180 days to define treatment discontinuation. This increase in gap better captures the true discontinuations vs. temporary lack of adherence [26].

All statistical analyses conducted in Brazil were performed using Stata software, version 15.1. Analyses conducted in Quebec were performed using SAS version 9.4 for UNIX (SAS Institute Inc., Cary, NC).

This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (process ETIC 0069.0.203.000-11) and by the McGill University Health Centre Ethics Review Board. Permission to link the data in Quebec was obtained from the Provincial Ethics Board, the Commission d'accès à l'information.

Results

Among the Brazilian patients who completed 1 year of follow-up, 15,481 were in the anti-TNF group (adalimumab 8,120, 52.4%; etanercept 4,901, 31.7%; and infliximab 2,460, 15.9%) and 3,838 in the cDMARD group. In the Quebec cohort, 983 were in the anti-TNF group (etanercept 398, 40.5%; adalimumab 304, 30.9%; golimumab 158, 16.1%; infliximab 85, 8.6%; and certolizumab 38; 3.9%) and 2,660 in the cDMARD group. Most patients from both the anti-TNF and cDMARD groups (Brazil: 53.2% and 66.8%; and Quebec: 65.0% and 61.0%) were enrolled in the cohort during the 2010- 2012 period (Table 1).

[Table 1 near here]

Brazilian patients were younger and more frequently males compared to Canadian patients. In the anti-TNF vs. cDMARD groups, the median (Q1–Q3) age were 41 (32–

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

50) vs. 43 (33–51) years and 64.3% vs. 60.1% were men. In Quebec, the median (Q1–Q3) ages were higher [64 (54–72) vs. 71 (62–78) years] and a lower proportion (30.3% vs. 31.7%) of men was observed.

With regard to socioeconomic status, for the anti-TNF and cDMARD groups, respectively the majority of Brazilian patients were from the two more developed regions of the country: Southeast (49.3% vs. 41.9) and Southern (21.8% vs. 36.0%). The median (Q1–Q3) municipal Gini index of patients were 0.53 (0.48–0.61) vs. 0.52 (0.47–0.61). In Quebec, 34.8% vs. 30.1% of patients were in the upper two social quintiles.

CCI was lower among Brazilians (mean \pm SD: 0.30 ± 0.77 vs. 0.28 ± 0.74) compared to those from Quebec (2.00 ± 1.79 vs. 2.34 ± 2.29). The Frailty index (mean in-hospital days in prior 2 years) was also lower among Brazilians (1.13 ± 7.68 vs. 1.57 ± 7.17) compared to Quebecers (3.96 ± 13.56 vs. 4.82 ± 18.44) (Table 1) in the respective treatment groups.

One-year persistence was less likely among Brazilian patients in both anti-TNF and cDMARDs groups (62.1 vs. 30.7 in Brazil and 66.9% vs 67.0 in Quebec). The mean \pm SD medication persistence in anti-TNF and cDMARDs groups were 293 ± 106 days vs. 213 ± 124 days in Brazil and 290 ± 104 days vs. 287 ± 108 days in Quebec (Tables 2-3).

[Tables 2 and 3 near here]

Among the Brazilian patients who completed 2 years of follow-up, 12,465 were in the anti-TNF group (6,430, 51.6% adalimumab; 3,969, 31.8% etanercept; and 2,066, 16.6% infliximab) and 3,344 in the cDMARD group. While in Quebec, 812 were in the anti-TNF group (332, 40.9% etanercept; 263, 32.4% adalimumab; 118, 14.5% golimumab;

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

74, 9.1% infliximab; and 25, 3.1% certolizumab) and 2,121 in the cDMARD group. In both countries, baseline characteristics of patients who completed the 2-year follow-up were similar to those of patients who completed the 1-year follow-up (Tables 2-3).

Persistence rates declined at the end of the second year of follow-up in both anti-TNF and cDMARD groups, but were still higher among the patients in Quebec (47.9% vs. 18.1% in Brazil and 51.5% vs. 53.5% in Quebec). The mean \pm SD medication persistence was 487 ± 257 vs. 294 ± 242 days for the anti-TNF vs. cDMARD groups, in Brazil and 454 ± 253 vs. 460 ± 259 days in Quebec (Tables 2-3). Persistence rates of individual anti-TNF drug rates are included in Tables 2-3. Since in our study we did not consider switching between cDMARDs as a treatment discontinuation, persistence was not assessed for the individual cDMARDs.

The Southern region of Brazil showed the highest proportion of persistent patients. The lowest proportions were observed in those who lived in the Northern and Northeast regions of Brazil. Medication persistence did not seem to differ between urban and rural areas, SES or year of cohort entry in Quebec.

The drug survival curves for the 2-years follow-up are shown in Figures 1 and 2. Overall, 50% of Brazilian patients discontinued therapy after 1.66 years in the anti-TNF group vs. 0.58 years in the cDMARD group ($P < 0.001$). Similar discontinuation rates in the anti-TNF and cDMARD groups were observed in Quebec at 2-year follow-up ($p = 0.78$).

[Figures 1 and 2 near here]

Multivariate Cox regression analyses for both the 1-year and 2-years follow-up among anti-TNF Brazilian users showed higher discontinuation rates in female patients, those

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

with higher municipal Gini index, residents of regions other than the Southern region, those with higher comorbidity score, and those who entered the cohort on or after January 1, 2013 (significant only in the 1-year follow-up analysis). While among Brazilian cDMARD users, younger patients and those with higher municipal Gini index, residents of the Northeast region, and patients enrolled on or after January 1, 2013 (significant only in the 1-year follow-up analysis) were more likely to discontinue therapy (Table 4). Multivariate Cox regression analyses among anti-TNF Quebec users showed lower discontinuation rates in older patients, while higher discontinuation rates among women and among corticosteroids and opioids users in the previous year. Among Quebec cDMARD users, older patients and those who used NSAIDs in the previous year were less likely to discontinue therapy at 1-year and at 2-year follow-up. Those who entered the cohort on or after January 1, 2013 were less likely to discontinue therapy at 1-year. In addition, patients with higher CCI were more likely to discontinue anti-TNF therapy in the 2-year follow-up (Table 4).

[Table 4 near here]

As expected, results of the sensitivity analyses allowing an interval gap of up to 180 days showed an increase in the overall proportion of persistent patients. Nevertheless, in both countries, the analyses performed did not substantially change the findings of the initial comparison between anti-TNF and cDMARD groups (Tables 5-6, supplement).

Discussion

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Our study assessed anti-TNFs and cDMARD therapy use in patients with AS in real world settings in Brazil and Quebec, Canada. We found that Canadians with AS were more likely than their Brazilian counterparts to persist on anti-TNF or cDMARDs therapy at 1 and 2-year follow-up, although rates were lower at 2 vs. 1 year in both countries. While similar persistence on anti-TNF and cDMARDs was observed in Quebec, higher persistence on anti-TNF was observed in Brazil. Golimumab and certolizumab persistence was only evaluated among Canadian patients. In Quebec, persistence at 1 and 2 years were better with golimumab and certolizumab compared to etanercept, adalimumab and infliximab, while in Brazil persistence was worst with infliximab vs. etanercept and adalimumab (golimumab and certolizumab were not covered by SUS in Brazil). In both Brazil and Quebec, women and those with higher comorbidity scores were more likely to discontinue anti-TNF treatment, while older anti-TNF and cDMARD users in Quebec and only cDMARD users in Brazil were less likely to discontinue their treatment. Persistence did not differ between geographical regions or socioeconomic status in Quebec, while in Brazil it increased with higher Human Development Index (HDI) [24] and lower Gini index suggesting the presence of socioeconomic disparity in access to health care and treatment in that country. Persistence at 1 year was worst among Brazilian patients who initiated anti-TNF or cDMARD treatment on or after January 1, 2013, while it was better among Quebecers who initiated cDMARD in that period.

Real-world studies assessing biologic therapy use in patients with AS are scarce in spite of the impact on AS morbidity and healthcare costs, including anti-TNFs costs [9,10,18,27]. High persistence was also reported among anti-TNF vs. cDMARDs users with AS in a multicountry study [28]. Another Brazilian study also found higher

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

persistence on anti-TNF vs. cDMARDs among individuals with AS [29]. Similar to our Canadian study, higher persistence on anti-TNF therapy were reported in a Slovenian (75%) [30] and a German study (72%) [31] at 1 year and in the Slovenian study at 2 years (65%)[30]. . Of note, another German study, showed a lower persistence (48%) at 1 year [19], as observed in our Brazilian study. Lower persistence rates on anti-TNF therapy among patients with AS were also observed in North American studies (40.6% at 1-year and 22.8% to 32.6 at 2-years) [2,32].

As found in our Canadian study, better persistence on golimumab was observed in other Canadian [18] and European studies [30,33], a result that may perhaps be partly explained by the simpler, less frequent dosing regimen of golimumab. Better certolizumab persistence was also observed in the European study [33], and similar persistence on etanercept and adalimumab were observed in other Canadian and European studies [18,33-35]. The worst persistence among Brazilian users of infliximab may perhaps be explained by its higher risk of adverse events [36] and the convenience of subcutaneous administered drugs. However contrary to our study, Flouri et al. observed higher retention rate with infliximab relative to adalimumab and etanercept at 6 months among Greek patients with spondyloarthritis; adalimumab was the anti-TNF best retained after the first 6 months [13].

Differences in study design, eligibility criteria, sample size, discontinuation definition, calendar period, reimbursement and patient co-payment policies between published studies may explain the difference in their reported studies. Many patients restart index therapy after a short treatment gap [37]. According to our sensitivity analysis, about one-fifth of all Quebec patients and 13% of Brazilian patients restarted therapy after

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

discontinuation in the 1-year follow-up. A similar proportion of patients in Quebec, but only a handful of patients in Brazil, restarted therapy after discontinuation in the second year of follow-up. The literature points to a lack of efficacy and adverse events as the main reasons of therapy discontinuation [13,18,38]. Many patients experiencing adverse events do not renew their prescription when symptoms subside [37]. Other reasons for discontinuation include intentional non-compliance, supply shortage, cost/affordability of treatment, patient misunderstanding of the treatment, and lack of social support [39]. Although, supply shortage may have occurred in Brazil in some areas, it was not an issue in Quebec. Anti-TNF and cDMARDs agents are covered by the public health system in both Quebec and Brazil, so persistence was unlikely affected by the cost of therapy in our study.

As in our study, several published studies have shown that persistence to anti-TNF agents was significantly worse in female compared to male patients with AS [13,28,31,39,40]. Suboptimal persistence may be due to lower clinical effectiveness in female patients [39]. Indeed,, female patients with AS had lower clinical response than male patients[27] and were less likely to achieve partial remission response after 1 year of anti-TNF therapy [41].

Our study found better persistence with older age with both anti-TNF and cDMARD in Quebec and with only cDMARDs in Brazil. However, persistence have been reported to deteriorate in the very old because of polypharmacy, lack of social support and impaired physical and intellectual functions [42]; these issues could not be assessed in our study.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

The socioeconomic disparity and the inequality in health care delivery observed in Brazil in our study was also reported in other Brazilian studies [43-45], and deserves further investigations. A French study also observed that non-persistent patients with AS were more likely to have lower socio-economic status [40].

Higher discontinuation rates during the first year of treatment in more recent years, and increasing discontinuation across calendar periods, have also been observed in a number of studies in patients with rheumatoid arthritis (RA) [22,46]. On the other hand, similar to our Canadian study, a cohort study of RA patients found that cDMARD users who entered the cohort more recently were less likely to discontinue medication [45]; reasons for the better persistence on cDMARDs in more recent years in Quebec are unknown. However, we should note that this result was marginally significant (95% CI; 0.74, 1.00 and p-value 0.048) and need to be confirmed in future studies.

Comorbidities have been related with discontinuation of therapy in studies of AS [39,40] and other rheumatic diseases [47,48]. Multiple comorbidities add to the burden of AS and the complexity of its management [49].

Our results must be considered in light of certain strengths. Our study is population-based. It used administrative data and reports real-world drug persistence. Pharmacy and medical record are considered one of the most objective and accurate methods for the assessment of adherence/persistence. Their use has become widespread in recent years, thanks to the increased availability of administrative health records which are valuable research tools [50]. Two large cohorts of AS patients were constructed using similar selection criteria which allowed comparison of anti-TNF and cDMARDs utilization patterns between the two countries. However, we acknowledge that our study has a number of limitations.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Firstly, the administrative data used have limited clinical information. As a result, information about disease activity/severity and clinical measures was typically not available; consequently, the reasons for treatment discontinuation could not be established. Secondly, residual confounding bias may also be an issue in spite of adjustment for factors known to be associated with discontinuation of therapy. Thirdly, it was not a goal of this study to evaluate persistence among anti-TNF switchers. Future studies should address this knowledge gap. Despite these limitations, we believe that our study appropriately assessed the utilization patterns of the two treatment regimens in AS patients assisted through the universal health systems in both Brazil and Quebec during the study period.

Conclusions

This is a population-based study that used health administrative data from Brazil and Quebec, Canada. It reports on real-world drug persistence. It is large in size and data coverage. These countries were chosen to provide contrasting settings although both provide comprehensive healthcare through different means. Canadian AS patients from Quebec showed better rates of medication persistence than Brazilian patients, in both 1-year and 2-years of follow-up. Age, sex and comorbidities had a significant influence on medication persistence in both countries. While medication persistence in Quebec did not seem to differ between geographical regions or socioeconomic status, in Brazil we found some differences associated with these characteristics, which may be related to inequities in the access to health care. These findings contribute to a better understanding of the the real-world treatment patterns of AS patients in both countries. This is important because

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

non-persistence can affect the success of therapeutic treatment, disease remission and disease severity as well as decrease the quality of life of patients.

Transparency

Declaration of funding

The authors did not receive financial support for this study. F.A. Acurcio is a research scholar funded by the National Counsel of Technological and Scientific Development (CNPq / Brazil, process 302137/2016-5). E. Rahme has received funds and consulting fees from Janssen Inc. in the course of an unrelated study. These institutions did not play any role in the design, the data collection, or the analysis of the study.

Author contributions

Acurcio FA and Rahme E designed the study, analysed the data and drafted the manuscript; Silva MRR, Guerra Jr AA, Pereira RG, Nedjar H extracted, prepared and analysed the data; Godman B and Bennie M were involved in the analysis and interpretation of the data; All authors revised the manuscript critically for intellectual content and did the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

Declaration of financial/other relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

References

1. Ulus Y, Akyol Y, Bilgici A, et al. Association of work instability with fatigue and emotional status in patients with ankylosing spondylitis: comparison with healthy controls. *Clin Rheumatol* 2019; 38:1017-24.
2. Walsh JA, Adejoro O, Chastek B, et al. Treatment patterns of biologics in US patients with ankylosing spondylitis: descriptive analyses from a claims database. *J Comp Eff Res* 2018; 7:369-80.
3. Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017; 390(10089):73-84.
4. Kotsis K, Voulgari PV, Drosos AA, et al. Health-related quality of life in patients with ankylosing spondylitis: a comprehensive review. *Expert Rev Pharmacoecon Outcomes Res* 2014; 14(6):857-72.
5. Rahman P, Choquette D, Bensen WG, et al. Biologic treatment registry across Canada (BioTRAC): a multicentre, prospective, observational study of patients treated with infliximab for ankylosing spondylitis. *BMJ Open* 2016; 6:e009661.
6. Stolwijk C, van Onna M, Boonen A, et al. Global prevalence of spondyloarthritis: a systematic review and meta-regression analysis. *Arthritis Care Res* 2016; 68:1320-31.
7. Dean LE, Jones GT, MacDonald AG, et al. Global prevalence of ankylosing spondylitis. *Rheumatol* 2014; 53:650-7.
8. Braun J, Sieper J. Ankylosing spondylitis. *Lancet* 2007; 369:1379-90.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

9. Kruger K, von Hinuber U, Meier F, et al. Ankylosing spondylitis causes high burden to patients and the healthcare system: results from a German claims database analysis. *Rheumatol Int* 2018; 38:2121-31.

10. Corbett M, Soares M, Jhuti G, et al. Tumour necrosis factor- α inhibitors for ankylosing spondylitis and non-radiographic axial spondyloarthritis: a systematic review and economic evaluation. *Health Technol Assess* 2016; 20:1-334.

11. Machado MA, Ferre F, Moura CS, et al. Costs of drug therapy in patients with ankylosing spondylitis in Brazil. *Rheumatol Ther* 2016; 3:353-61.

12. Malinowski KP, Kawalec P. The indirect costs of ankylosing spondylitis: a systematic review and meta-analysis. *Expert Rev Pharmacoecon Outcomes Res* 2015; 15:285-300.

13. Flouri ID, Markatseli TE, Boki KA. Comparative analysis and predictors of 10-year tumor necrosis factor inhibitors drug survival in patients with spondyloarthritis: first-year response predicts long term drug persistence. *J Rheumatol* 2018; 45:6.

14. van der Heijde D, Ramiro S, Landewé R, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017; 76:978-91.

15. Maxwell LJ, Zochling J, Boonen A, et al. TNF-alpha inhibitors for ankylosing spondylitis. *Cochrane Database Syst Rev* 2015; 4:Cd005468

16. Mercer LK, Askling J, Raaschou P, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. *Ann Rheum Dis* 2017; 76:386-91

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

17. Acar M, Juneja P, Handel M. Treatment persistence of subcutaneous TNF inhibitors among Australian patients with immune-mediated rheumatic disease (iMRD). *Open Access Rheumatol* 2018; 10:151-60.

18. Bhoi P, Bessette L, Bell MJ, et al. Adherence and dosing interval of subcutaneous antitumour necrosis factor biologics among patients with inflammatory arthritis: analysis from a Canadian administrative database. *BMJ Open* 2017; 7:e015872.

19. Lyu R, Govoni M, Ding Q, et al. Treatment persistence among patients with rheumatoid disease (RA, AS, PsA) treated with subcutaneous biologics in Germany. *Rheumatol Int* 2016; 36:143-53.

20. Putrik P, Ramiro S, Kvien TK, et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. *Ann Rheum Dis* 2014; 73:198-206

21. Guerra AA Jr, Pereira RG, Gurgel EI, et al. Building the national database of health centred on the individual: administrative and epidemiological record linkage - Brazil, 2000-2015. *Int J Popul Data Sci* 2018; 3:3:20.

22. Neovius M, Arkema EV, Olsson H, et al. Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab. *Ann Rheum Dis* 2015; 74:354–60.

23. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-9

24. UNDP United Nations Development Programme, IPEA Institute for Applied Economic Research, and JPF João Pinheiro Foundation. Atlas of Human Development in

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Brazil 2013, UNDP, IPEA, and JPF (2014), <http://www.atlasbrasil.org.br/2013/en/home/> (accessed May 21, 2019).

25. Pampalon R, Hamel D, Gamache P, et al. A deprivation index for health planning in Canada. *Chronic Dis Can* 2009; 29:178-91

26. Fisher A, Bassett K, Wright JM, et al. Comparative persistence of the TNF antagonists in rheumatoid arthritis – a population-based cohort study. *PLoS ONE* 2014; 9: e105193.

27. Machado MA, Almeida AM, Kakehasi AM, et al. Real life experience of first course of anti-TNF treatment in ankylosing spondylitis patients in Brazil. *Rheumatol Ther* 2016; 3:143-54.

28. Smolen JS, Gladman D, McNeil HP, et al. Predicting adherence to therapy in rheumatoid arthritis, psoriatic arthritis or ankylosing spondylitis: a large cross-sectional study. *RMD Open* 2019; 5:e000585.

29. Machado MAA, Moura CS, Ferre F, et al. Treatment persistence in patients with rheumatoid arthritis and ankylosing spondylitis. *Rev Saude Publica* 2016; 50:50.

30. Rotar Z, Tomsic M, Praprotnik S. The persistence of golimumab compared to other tumour necrosis factor- α inhibitors in daily clinical practice for the treatment of rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: observations from the Slovenian nation-wide longitudinal registry of patients treated with biologic disease-modifying antirheumatic drugs—BioRx.si. *Clin Rheumatol* 2019; 38:297-305.

31. Jacob L, Chevalier T, Kostev K. Persistence with biological drugs in patients treated in rheumatology practices in Germany. *Rheumatol Int* 2019; 39:525-31.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

32. Hunter T, Deodhar AA, Bolce R, et al. Predicting treatment persistence and non-persistence of newly initiated TNF inhibitor therapy in ankylosing spondylitis patients: a gender comparison [abstract]. *Arthritis Rheumatol* 2018; 70:Suppl10.

33. Belhassen M, Hudry C, Woronoff MC, et al. Treatment persistence with subcutaneous TNF-alpha inhibitors in France [abstract]. *Arthritis Rheumatol* 2016; 68:Suppl 10.

34. Dalén J, Svedbom A, Black CM, et al. Treatment persistence among patients with immune-mediated rheumatic disease newly treated with subcutaneous TNF-alpha inhibitors and costs associated with non-persistence *Rheumatol Int* 2016; 36:987-95.

35. Takacs P, Iathia U, Shin J, et al. Persistence to subcutaneous biological agents in Hungarian patients treated for inflammatory arthritis. *Patient Prefer Adherence* 2019; 13:157–63

36. Desai RJ, Thaler KJ, Mahlknecht P, et al. Comparative risk of harm associated with the use of targeted immunomodulators: a systematic review. *Arthritis Care Res* 2016; 68:1078-88.

37. Kostev K, Jacob L. Persistence and treatment-free interval in patients being prescribed biological drugs in rheumatology practices in Germany. *Eur J Clin Pharmacol* 2019; 75:717-22.

38. García-Lagunar MH, Gutiérrez-Cívicos MR, García-Simón MS, et al. Reasons for discontinuation and adverse effects of TNF α inhibitors in a cohort of patients with rheumatoid arthritis and ankylosing spondylitis. *Ann Pharmacother* 2017; 51: 388-93.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

39. Maniadas N, Toth E, Schiff M, et al. A targeted literature review examining biologic therapy compliance and persistence in chronic inflammatory diseases to identify the associated unmet needs, driving factors, and consequences. *Adv Ther* 2018; 35:1333-55.

40. Fautrel B, Belhassen M, Hudry C, et al. Determinants of 12-months persistence in ankylosing spondylitis patients initiating subcutaneous TNF-alpha inhibitors [abstract]. *Ann Rheum Dis* 2017; 76:754-55.

41. Perrotta FM, Addimanda O, Ramonda R, et al. Predictive factors for partial remission according to the Ankylosing Spondylitis Assessment Study working group in patients with ankylosing spondylitis treated with anti-TNF α drugs. *Reumatismo* 2014; 66:208–14.

42. Wheeler KJ, Roberts ME, Neiheisel MB. Medication adherence part two: predictors of nonadherence and adherence. *J Am Assoc Nurse Pract* 2014; 26:225-32.

43. Travassos C, Oliveira EXG, Viacava F. Geographic and social inequalities in the access to health services in Brazil: 1998 and 2003. *Cien Saude Colet* 2006; 11:975-86.

44. Machado EL, Caiaffa WT, Cesar CC, et al. Iniquities in the access to renal transplant for patients with end-stage chronic renal disease in Brazil. *Cad Saude Publica* 2011; 27:s284-s297

45. Acurcio FA, Machado MA, Moura CS, et al. Medication persistence of disease-modifying antirheumatic drugs and anti-tumor necrosis factor agents in a cohort of patients with rheumatoid arthritis in Brazil. *Arthritis Care Res* 2016; 68:1489-96.

46. Gómez-Reino JJ, Rodríguez-Lozano C, Campos-Fernandez C, et al. Change in the discontinuation pattern of tumour necrosis factor antagonists in rheumatoid arthritis over

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

10 years: data from the Spanish registry BIOBADASER 2.0. *Ann Rheum Dis* 2012; 71:382–5.

47. Ogale S, Hitraya E, Henk HJ. Patterns of biologic agent utilization among patients with rheumatoid arthritis: a retrospective cohort study. *BMC Musculoskelet Disord* 2011; 12:204.

48. Markenson JA, Gibofsky A, Palmer WR, et al. Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS Registry. *J Rheumatol* 2011; 38:1273-81.

49. Mercieca C, van der Horst-Bruinsma IE, Borg AA. Pulmonary, renal and neurological comorbidities in patients with ankylosing spondylitis; implications for clinical practice. *Curr Rheumatol Rep* 2014; 16:434.

50. Malo S, Kardas P, Menditto E. Some reflections concerning the assessment of patient adherence and persistence to medication, *Curr Med Res Opin* 2019, 35:1, 3-4.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Table 1 Baseline characteristics of patients with ankylosing spondylitis who had at least one full year of follow-up

Variables	Brazil		Quebec, Canada	
	cDMARD-only N= 3,838	Anti-TNF (+/- cDMARD) N= 15,481	cDMARD-only N= 2,660	Anti-TNF (+/- cDMARD) N= 983
Age (years)				
Median (Q1-Q3)	43 (33-51)	41 (32-50)	71 (62-78)	64 (54-72)
20-25	295 (7.7)	1,252 (8.1)	19 (0.7)	8 (0.8)
26-35	908 (23.7)	4,011 (25.9)	51 (1.9)	41(4.2)
36-45	1,087 (28.3)	4,492 (29.0)	92 (3.5)	75 (7.6)
46-55	950 (24.8)	3,575 (23.1)	264 (9.9)	169 (17.2)
56-65	448 (11.7)	1,646 (10.6)	453 (17.0)	256 (26.0)
66 +	150 (3.9)	505 (3.3)	1,781 (67.0)	434 (44.2)
Sex (male, n (%))	2,305 (60.1)	9,955 (64.3)	844 (31.7)	298 (30.3)
Region of residence, n (%)				
Northern	91 (2.4)	455 (2.9)	-	-
Northeast	550 (14.3)	2,419 (15.6)	-	-
Central-West	208 (5.4)	1,608 (10.4)	-	-
Southern	1,381 (36.0)	3,373 (21.8)	-	-
Southeast	1,608 (41.9)	7,626 (49.3)	-	-
Rural	-	-	442 (16.6)	235 (23.9)

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Urban	-	-	2,218 (83.4)	748 (76.1)
Municipal Gini index*				
Median (Q1-Q3)	0.52 (0.47 - 0.61)	0.53 (0.48 - 0.61)		
Socioeconomic status				
quintiles n (%) [§]				
1	-	-	370 (13.9)	160 (16.3)
2	-	-	431 (16.2)	182 (18.5)
3	-	-	522 (19.6)	165 (16.8)
4	-	-	544 (20.5)	188 (19.1)
5	-	-	566 (21.3)	217 (22.1)
Calendar period of cohort				
entry, n (%)				
2010 – 2012	2,565 (66.8)	8,238 (53.2)	1,622 (61.0)	639 (65.0)
≥ 2013	1,273 (33.2)	7,243 (46.8)	1,038 (39.0)	344 (35.0)
Patients with				
comorbidities, n (%)	793 (20.6)	3,661 (23.6)	2,496 (93.8)	922 (93.8)
Charlson comorbidity				
score, mean (SD)	0.28 (0.74)	0.30 (0.77)	2.34 (2.29)	2.00 (1.79)

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Patients with previous				
hospitalization‡, n (%)	584 (15.2)	1,627 (10.3)	872 (32.8)	341 (34.7)
General patient				
frailty‡, mean (SD)	1.57 (7.17)	1.13 (7.68)	4.82 (18.44)	3.96 (13.56)
NSAID use in prior year	-	-	1,807 (67.9)	627 (63.8)
Corticosteroid use in prior				
year	-	-	1,843 (69.3)	681 (69.3)
Opioid use in prior year	-	-	786 (29.5)	349 (35.5)

* Municipal Gini Index according to the municipal mesh existent in 2010, Brazil.

§ 227 patients in the cDMARD group and 71 in the Anti-TNF (+/- cDMARD) group had 'undetermined' socioeconomic quintile.

‡ In-hospital days, assessed during the two years preceding baseline.

Q1-Q3: lower quartile-upper quartile.

cDMARD: conventional disease-modifying anti-rheumatic drugs; TNF: tumor necrosis factor

NSAID: Nonsteroidal anti-inflammatory drug

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Table 2. Medication persistence and proportion of persistent patients by selected characteristics in the Brazilian ankylosing spondylitis cohort, 2010–2015*

Follow-up	First year of follow-up †		First two years of follow-up ‡	
	cDMARD-only N=3,838	Anti-TNF (+/- cDMARD) N=15,481	cDMARD-only N= 3,344	Anti-TNF (+/- cDMARD) N= 12,465
Medication persistence (mean ± SD, days) §	213±124	293±106	294±242	487±257
Persistent patients, n (%)				
all patients	1178 (30.7)	9618 (62.1)	605 (18.1)	5968 (47.9)
by anti-TNF dispensed				
adalimumab (+/- cDMARD)	-	5158 (63.5)	-	3192 (49.6)
etanercept (+/- c DMARD)	-	3177 (64.8)	-	2054 (51.8)
infliximab (+/- cDMARD)	-	1283 (52.2)	-	722 (35.0)
by region of residence				
Northern	23 (25.3)	215 (47.2)	11 (12.5)	109 (31.8)

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Northeast	93 (16.9)	1122 (46.4)	43 (8.9)	557 (27.9)
Central-West	48 (23.1)	1020 (63.4)	32 (16.8)	647 (49.3)
Southern	515 (37.3)	2397 (71.1)	271 (22.5)	1597 (57.4)
Southeast	499 (31.0)	4864 (63.8)	248 (18.0)	3058 (50.7)
by Municipal Gini index				
< 0.53	709 (34.7)	4859 (67.0)	379 (21.6)	3132 (54.2)
≥ 0.53	469 (26.2)	4758 (57.8)	226 (14.2)	2835 (42.4)
by calendar period				
2010 – 2012	843 (32.9)	5337 (64.8)	493 (19.2)	4017 (48.8)
≥ 2013#	335 (26.3)	4281 (59.1)	112 (14.4)	1951 (46.2)

* Values are the number (%) unless indicated otherwise, and the proportions were calculated using the number of individuals in each category as the denominator. cDMARD = conventional disease-modifying antirheumatic drug; TNF = tumor necrosis factor. † Patients with < 1 year of follow-up were excluded from this analysis. ‡ Patients with < 2 years of follow-up were excluded from this analysis. § Drug-free interval of up to 60 days. #2013-2014 for the 1-year follow-up and 2013 for the 2-year follow-up

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Table 3. Medication persistence and proportion of persistent patients by selected characteristics in the Quebec ankylosing spondylitis cohort, 2010–2015*

Follow-up	First year of follow-up †		First two years of follow-up ‡	
	cDMARD-only N=2,660	Anti-TNF (+/- cDMARD) N=983	cDMARD-only N= 2,121	Anti-TNF (+/- cDMARD) N= 812
Medication persistence (mean ± SD, days) §	287 ±108	290 ± 104	460 ± 259	454 ± 253
Persistent patients, n (%)				
all patients	1,782 (67.0)	658 (66.9)	1,135 (53.5)	418 (51.5)
by anti-TNF dispensed				
Adalimumab (+/- cDMARD)	-	198 (65.1)	-	130 (49.4)
Etanercept (+/- cDMARD)	-	257 (64.6)	-	165 (49.7)
Infliximab (+/- cDMARD)	-	56 (65.9)	-	36 (48.6)
Golimumab (+/- cDMARD)		121 (76.6)		72 (61.0)

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Certolizumab (+/- cDMARD)		26 (68.4)		15 (60.0)
by region of residence				
Rural	304 (68.8)	158 (67.2)	187 (54.4)	99 (51.0)
Urban	1,478 (66.6)	500 (66.8)	948 (53.3)	319 (51.6)
by socioeconomic status				
1	256 (69.2)	103 (64.4)	175 (60.6)	72 (50.0)
2	305 (70.8)	117 (64.3)	186 (54.9)	66 (43.7)
3	361 (69.2)	113 (68.5)	235 (57.3)	72 (56.3)
4	359 (66.0)	135 (71.8)	236 (54.1)	86 (55.1)
5	362 (64.0)	144 (66.4)	217 (47.5)	93 (54.1)
by calendar period				
2010-2012	1,059 (65.3)	434 (67.9)	853 (52.6)	337 (52.7)
≥ 2013#	723 (69.7)	224 (65.1)	282 (56.5)	81 (46.8)

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

* Values are the number (%) unless indicated otherwise, and the proportions were calculated using the number of individuals in each category as the denominator. cDMARD = conventional disease-modifying antirheumatic drug; TNF = tumor necrosis factor. † Patients with < 1 year of followup were excluded from this analysis. ‡ Patients with < 2 years of followup were excluded from this analysis. § Drug-free interval of up to 60 days. # 2013-2014 for the 1-year follow-up and 2013 for the 2-year follow-up.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Table 4. Factors associated with discontinuation of therapy: Cox regression models*

Variables		cDMARD – only		Anti-TNF (+/- cDMARD)	
		First year of follow-up	First 2 years of follow-up	First year of follow-up	First 2 years of follow-up
Brazil					
Age (1 year increase)		0.995 (0.992 -0.998)	0.997 (0.994 – 0.999)	-	-
Sex	<i>Female</i>	-	-	1.22 (1.16 - 1.29)	1.22 (1.16 - 1.29)
	<i>Male</i>	-	-	1.00 (ref)	-
Region of residence	<i>Northern</i>	1.24 (0.96 – 1.61)	1.19 (0.93 – 1.52)	2.06 (1.78 - 2.39)	1.88 (1.62 – 2.18)
	<i>Northeast</i>	1.46 (1.28 – 1.67)	1.37 (1.20 – 1.57)	2.08 (1.89 – 2.28)	2.04 (1.87 – 2.23)
	<i>Central-West</i>	1.24 (1.03 – 1.49)	1.10 (0.92 – 1.32)	1.25 (1.12 - 1.39)	1.17 (1.06 – 1.29)
	<i>Southeast</i>	1.08 (0.99 – 1.19)	1.05 (0.96 – 1.15)	1.26 (1.17 - 1.36)	1.19 (1.11 – 1.27)
	<i>Southern</i>	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Gini index†		2.72 (1.47 – 5.03)	3.77 (2.06 – 6.91)	2.18 (1.43 – 3.33)	2.95 (1.98 – 4.40)
CCI‡		-	-	1.09 (1.07 - 1.12)	1.08 (1.06 – 1.10)
Calendar period	≥ 2013#	1.14 (1.06 – 1.24)	-	1.18 (1.12 – 1.24)	-

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

		2010 - 2012	1.00 (ref)	-	1.00 (ref)	-
Quebec, Canada						
Age (1 year increase)		0.986 (0.981 -0.992)	0.987 (0.982 -0.992)	0.989 (0.981 -0.998)	0.988 (0.981 -0.996)	
Sex	<i>Female</i>	-	-	1.41 (1.08-1.83)	-	
	<i>Male</i>	-	-	1 (ref)	-	
CCI‡		-	-	-	1.06 (1.00 – 1.12)	
Calendar period	<i>≥ 2013#</i>	0.86 (0.74 – 1.00)	-	-	-	
	<i>2010-2012</i>	1.00 (ref)	-	-	-	
	<i>Nonsteroidal</i>			-		
Medications in prior	<i>antiinflammatory</i>					
year	<i>drugs</i>	0.71 (0.61- 0.82)	0.74 (0.64-0.86)			-
	<i>Corticosteroids</i>	-	-	1.36 (1.04 – 1.78)	1.34 (1.06 – 1.70)	
	<i>Opioids</i>	-	-	1.39 (1.10 – 1.75)	1.41 (1.14 – 1.74)	

* Values are adjusted hazard ratio (95% confidence interval). Hazard ratios >1 indicate more likely to discontinue therapy. cDMARD = conventional disease-modifying antirheumatic drug; TNF = tumor necrosis factor; ref = reference. † Municipal Gini Index according to the

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

municipal mesh existent in 2010, Brazil; ‡ CCI = Charlson Comorbidity Index. #2013-2014 for the 1-year follow-up and 2013 for the 2-year follow-up

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

[supplementary material] Table 5. Sensitivity analysis: medication persistence and proportion of persistent patients, where a drug-free interval of up to 180 days was used, Brazilian ankylosing spondylitis cohort, 2010–2015*

Follow-up	First year of follow-up †		First two years of follow-up ‡	
	cDMARD-only N=3838	Anti-TNF (+/- cDMARD) N=15518	cDMARD-only N= 3205	Anti-TNF (+/- cDMARD) N= 11704
Medication persistence (mean ± SD, days) §	238±122	310±95	346±254	538±245
Persistent patients, n (%)				
all patients	1476 (38.5)	10690 (68.9)	644 (20.1)	5955 (50.9)
by anti-TNF dispensed				
adalimumab (+/- cDMARD)	-	5648 (69.4)	-	3081 (51.5)
etanercept (+/- cDMARD)	-	3495 (71.1)	-	2027 (53.8)
infliximab (+/- cDMARD)	-	1547 (62.8)	-	847 (43.3)
by region of residence				
Northern	40 (44.0)	260 (57.1)	17 (19.5)	110 (35.6)

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Northeast	150 (27.3)	1377 (56.8)	47 (10.2)	653 (35.0)
Central-West	70 (33.6)	1148 (71.4)	35 (19.2)	666 (53.6)
Southern	585 (42.4)	2633 (77.7)	266 (23.0)	1572 (60.2)
Southeast	631 (39.2)	5272 (69.0)	279 (21.2)	2954 (52.1)
by Municipal Gini index				
< 0.53	850 (41.6)	5271 (72.5)	377 (22.5)	3015 (55.7)
≥ 0.53	626 (34.9)	5419 (65.7)	267 (17.5)	2940 (46.7)
by calendar period				
2010 - 2012	1049 (40.9)	5977 (72.6)	538 (21.0)	4343 (52.7)
≥ 2013#	427 (33.5)	4713 (64.7)	106 (16.6)	1612 (46.5)

* Values are the number (%) unless indicated otherwise, and the proportions were calculated using the number of individuals in each category as the denominator. cDMARD = conventional disease-modifying antirheumatic drug; TNF = tumor necrosis factor. † Patients with < 1 year of follow-up were excluded from this analysis. ‡ Patients with < 2 years of follow-up were excluded from this analysis. § Drug-free interval of up to 180 days. #2013-2014 for the 1-year follow-up and 2013 for the 2-year follow-up

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

[supplementary material] Table 6. Sensitivity analysis: medication persistence and proportion of persistent patients, where a drug-free interval of up to 180 days was used as a grace period between two dispensed prescriptions, Quebec ankylosing spondylitis cohort, 2010–2015*

Follow-up	First year of follow-up †		First two years of follow-up ‡	
	cDMARD-only N=2,660	Anti-TNF (+/- cDMARD) N=983	cDMARD-only N= 2,121	Anti-TNF (+/- cDMARD) N= 812
Medication persistence (mean ± SD, days) §	325±75	321±81	531±222	516±227
Persistent patients, n (%)				
all patients	2129 (80.0)	763 (77.6)	1380 (65.1)	489 (60.2)
by anti-TNF dispensed				
Adalimumab (+/- cDMARD)	-	230 (75.7)	-	155(58.9)
Etanercept (+/- cDMARD)	-	302 (75.9)	-	194 (58.4)
Infliximab (+/- cDMARD)	-	63 (74.1)	-	44 (59.5)
Golimumab (+/- cDMARD)		135 (85.4)		79 (66.9)
Certolizumab (+/- cDMARD)		33 (86.8)		17 (68.0)

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

by region of residence

Rural	356 (80.5)	184 (78.3)	229 (66.6)	117 (60.3)
Urban	1,773 (79.9)	579 (77.4)	1,151 (64.8)	372 (60.2)

by SES

1	300 (81.1)	125 (78.1)	206 (71.3)	87 (60.4)
2	351 (81.4)	137 (75.3)	226 (66.7)	80 (53.0)
3	433 (83.0)	130 (78.8)	284 (69.3)	83 (64.8)
4	444 (81.6)	155 (82.4)	289 (66.3)	101 (64.7)
5	436 (77.0)	164 (75.6)	271 (59.3)	105 (61.0)

by calendar period

2010-2012	1,282 (79.0)	504 (78.9)	1,035 (63.8)	390 (61.0)
≥ 2013 [#]	847 (81.6)	259 (75.3)	345 (69.1)	99 (57.2)

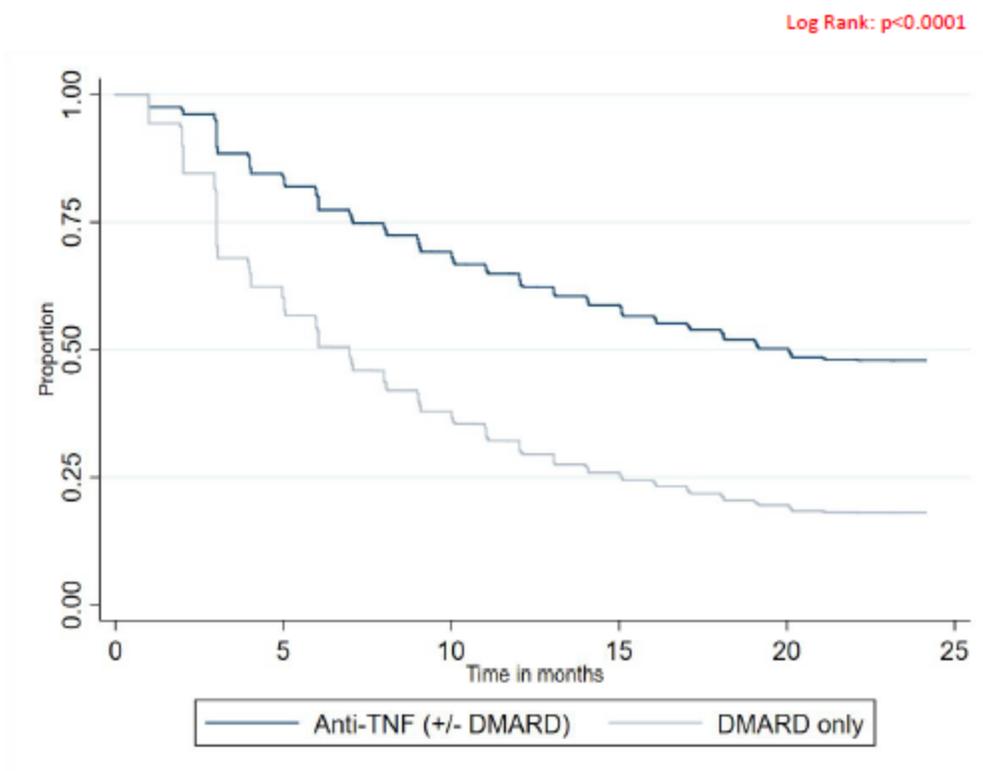
* Values are the number (%) unless indicated otherwise, and the proportions were calculated using the number of individuals in each category as the denominator. cDMARD = conventional disease-modifying antirheumatic drug; TNF = tumor necrosis factor. † Patients

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

with < 1 year of follow-up were excluded from this analysis. ‡ Patients with < 2 years of follow-up were excluded from this analysis. §

Drug-free interval of up to 180 days. . #2013-2014 for the 1-year follow-up and 2013 for the 2-year follow-up

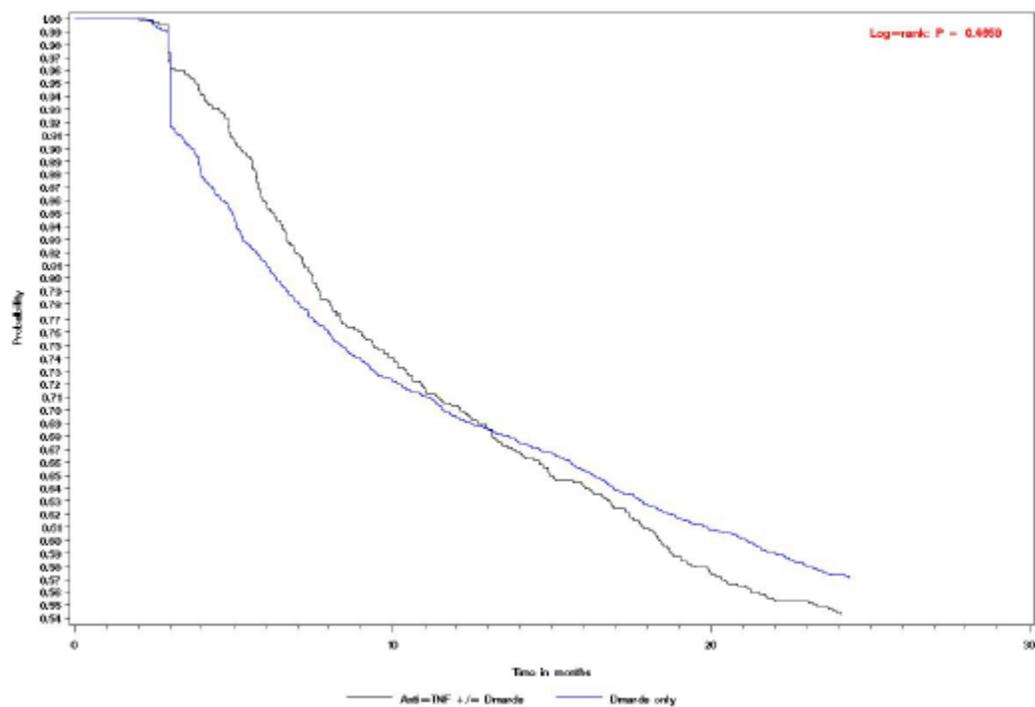
Figure 1. Drug survival by anti-tumor necrosis factor (anti-TNF) and conventional disease-modifying antirheumatic drug (cDMARD) initiation period. First 2 years follow-up, Brazil



This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.

Figure 2. Drug survival by anti-tumor necrosis factor (anti-TNF) and conventional disease-modifying antirheumatic drug (cDMARD) initiation period. First 2 years follow-up, Quebec, Canada



This is a peer-reviewed, accepted author manuscript of the following research article: Acurcio, F. D. A., Guerra Júnior, A. A., da Silva, M. R. R., Gonçalves Pereira, R., Godman, B., Bennie, M., ... Rahme, E. (Accepted/In press). Comparative persistence of anti-tumor necrosis factor therapy in ankylosing spondylitis patients: a multicenter international study. *Current Medical Research and Opinion*.