Research Article

Hospitalization for musculoskeletal disorders in rheumatoid arthritis patients: a population-based study

Marina Amaral de Ávila Machado1,2, Sasha Bernatsky1,3, Louis Bessette4, Hacene Nedjar1 and Elham Rahme1,3*

Abstract

Background: Rheumatoid arthritis (RA) patients failing disease modifying antirheumatic drugs (DMARDs) may undergo anti-Tumor Necrosis Factor (anti-TNF) therapy. Using the Quebec health services administrative databases, we examined the rates of musculoskeletal (MSD)-related hospitalizations among RA patients receiving anti-TNF, DMARDs, and neither of those therapies (non-users).

Methods: Matched cohort analyses were performed separately in 2002–2006 and 2007–2011. In each cohort, DMARD and non-user groups were formed to 3-1 match the anti-TNF users on age, sex, date of RA diagnosis, high-dimensional propensity score and date of the first anti-TNF dispensation (index-date). Non-users did not use DMARDs or anti-TNF drugs during the year before the index-date and in the 90 days post, but used at least one of these medications in the study period.

Results: During 2002–2006, 557 anti-TNF users were matched to 1144 DMARD users and to 656 non-users, compared to 690, 1651, and 532 patients, respectively during 2007–2011. The crude rates of MSD-related hospitalizations in the anti-TNF, DMARD and non-users groups were respectively: 8.2/100, 6.4/100 and 10.5/100 patient-years in 2002–2006, and 6.9/100, 4.8/100, and 8.6/100 patient-years in 2007–2011. In multivariable Cox regression models, the hazard ratios of MSD-related hospitalizations (95% confidence interval) were: 0.95 (0.60; 1.50) for anti-TNF and 0.69 (0.46; 1.02) for DMARD users, versus non-users in 2002–06, and 0.65 (0.37; 1.14) and 0.40 (0.24; 0.66), respectively in 2007–2011.

Conclusion: The MSD-related hospitalization risk was lower in RA patients using DMARD therapy and similar in those using anti-TNF therapy with or without DMARDs as compared to those not using either of these therapies during the study period.

Keywords: Rheumatoid arthritis, DMARDs, Anti-TNF, Musculoskeletal conditions

Background

Clinical practice guidelines recommend that disease-modifying anti-rheumatic drugs (DMARD) be introduced in rheumatoid arthritis (RA) as soon as possible. Combination therapy with DMARDs (methotrexate +/-hydroxychloroquine +/- sulfasalazine) and/or the addition of biologic agents that target Tumor Necrosis Factor (TNF) is considered in patients who have an inadequate response to DMARD monotherapy. Corticosteroids are also used, to manage flares and suppress symptoms [1].

In Quebec, anti-TNF drugs were listed on the public drug formulary for RA in 2002. Eligibility for an anti-TNF remains active synovitis (eight or more joints), and having failed two DMARDs including methotrexate [2]. As such, anti-TNF drug users would be expected to have more severe RA compared to non-
users, with a trend towards more prompt initiation in more recent times [3–5].

Randomized controlled trials (RCT) and observational studies have demonstrated benefits of anti-TNF agents in RA treatment on the basis of both disease activity and joint damage [6, 7]. Some observational studies have considered hospital admissions as an effectiveness indicator showing that anti-TNF therapy may reduce the rate of hospitalization, although the results remain uncertain [8, 9].

We used a high-dimensional propensity score approach [10] with Quebec health services administrative data to compare the rates of musculoskeletal (MSD)–related hospitalizations among RA patients receiving anti-TNF therapy, those receiving DMARDs, and those patients who were receiving neither of those therapies (non-users). We also compared results across calendar time. We hypothesized that MSD-related hospital admission rates were lower in RA patients using anti-TNF agents compared to patients using DMARDs.

Methods
Data sources
We used physician and prescription drug claims, hospital discharge data, and demographic records from January 1997 to March 2012 from the provincial health services administrative databases administered by the Régie de l’assurance maladie du Québec (RAMQ). In this Canadian province, coverage for outpatient and inpatient physician services is provided for the entire population (about 7.5 million people). Individuals aged 65 years or older (1,106,428 individuals in 2011; 90% of that population) and those under 65 years (2,261,786 individuals in 2011; 32% of that population) were included. The DMARDs included in the study were: auranofine, sulfasalazine, leflunomide, aurothioglucose, cyclosporine, methotrexate, minocycline, penicillamine, auranofine, sulfasalazine, leflunomide, aurothioglucose, aurothiomalate. Other non-anti-TNF biologic drugs were not included in this study because of the very small number of users.

Study cohorts
Each study cohort consisted of three groups, anti-TNF, DMARDs and non-users. Patients in the RA cohort dispensed an anti-TNF in 2002–2006 were identified at the first dispensation date (index date). Those covered by the provincial drug plan for at least 1 year prior and 3 months post the index date were included and formed the anti-TNF group (anti-TNF naïve in the previous year). Two other groups, the DMARD and non-user groups, were formed to match the anti-TNF group (anti-TNF naïve in the previous year). To form the DMARD group, for each individual in the anti-TNF group, three anti-TNF naïve individuals (for at least 1 year before and 90 days after the date of anti-TNF
dispensing) who used a DMARD within 90 days of the index date of the anti-TNF individual were selected at random from those eligible at the date of the DMARD use (index date; for those who used more than one DMARD within the 90-day-period, the closest date to the anti-TNF index date was chosen). The non-user group was constructed similarly. For each individual in the anti-TNF group, three anti-TNF and DMARD naïve individuals were selected at random to match the anti-TNF individual on age, sex, date of RA and high-dimensional propensity score as described above. The index date of the anti-TNF individual was assigned as the index date of the non-user individuals. Of note, patients in the non-user group did not use an anti-TNF or a DMARD for at least 1 year before and 90 days after the index date, but have used at least one of these drugs at another time during the study period as described above. The non-users could be under therapy with other drugs, such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs). The high-dimensional propensity score has been proposed to adjust for indication and confounding biases caused by missing or misclassified information. In this study, the high-dimensional propensity score (probability of receiving an anti-TNF) was calculated in a multivariate logistic regression model adjusted for a large number of covariates (500), as suggested in the algorithm, assessed based on all diagnoses, procedures, services and drug-dispensations recorded in the databases and selected according to their potential to bias the exposure-outcome relationship under study [10]. A high-dimensional propensity score algorithm is available as downloadable SAS software files from the Brigham and Women’s Hospital [13]. All included patients were required to be alive for at least 90 days past their index date and not to have had any MSD-related hospitalization in the prior year.

All study patients were followed from index date until the first date of death, end of drug coverage, switch/discontinuation of their index treatment or a maximum of 1 year. Discontinuation of treatment was defined as at least 90 days without the treatment and treatment switch was a switch between the three exposure groups (a switch between two DMARDS or two anti-TNFs was not considered to be a treatment switch).

Outcomes

The first hospitalization with a principal diagnosis for any MSD reason, ICD-9 and 10 codes included in the chapter XIII - diseases of the MSD system and connective tissue, during follow-up was the principal outcome (Appendix 1 and Appendix 2– diagnoses found in the study).

Patient baseline characteristics

Patient characteristics assessed at index date included: age, sex, type of insurance plan (based on patient eligibility for premium subsidies; low income patients were those receiving premium or partial subsidies), region of residence (urban or rural), visits to a rheumatologist in the prior year, comorbidity (cancer, ischemic heart disease, congestive heart failure (CHF), peptic ulcer disease, cerebrovascular disease (CVD), atrial fibrillation, and hematologic disorders), medication used in the prior year [corticosteroids, gastroprotective agents (proton pump inhibitors, misoprostol and histamine-2 receptor blocker), serotonin reuptake inhibitors (SSRI), anticoagulants, anti-diabetics, antihypertensives and NSAIDs]. These factors were chosen because of their potential association with the choice of RA treatment and the outcome (MSD-related hospitalizations). In addition, our data included an index of socioeconomic status (SES), with sub-indices of social and material deprivation, that was developed by the Institut National de Santé Publique du Québec on the basis of census enumeration area data on education level, employment/population ratio, and average income [14, 15].

Secondary analyses

In secondary analyses, patient selection, variable assessment and statistical analyses described above were repeated for patients on DMARDS and patients on neither drug, in the three periods (1998–2001, 2002–2006 and 2007–2011). The DMARD group in this analysis consisted of all patients who used a DMARD, but had never been on an anti-TNF prior to the DMARD use, as opposed to the previous analysis where the DMARD group was selected to match the anti-TNF group.

Statistical analyses

The following analyses were conducted separately in each of the study periods. Descriptive analyses [mean and standard deviation (SD) or proportion] were used as appropriate to report baseline patient characteristics by treatment group. Polytomous logistic regression models were used to compare patient baseline characteristics between the three treatment groups. The crude rates/100 patient-years (py) of MSD-related hospitalizations were assessed. Kaplan Meier curve displayed time to the first MSD-related hospitalization in the three treatment groups. Multivariable Cox proportional hazard models were used to compare the hazard ratios of MSD-related hospitalizations between treatment groups adjusting for patient baseline characteristics.
All statistical analyses described above were repeated in secondary analyses to compare MSD-related hospitalizations in the DMARD users versus non-users in the three time-periods. All statistical analyses were performed using SAS version 9.4 for UNIX (SAS Institute Inc., Cary, NC).

Results
In total, 10,418 RA individuals were in the 2002–2006 cohort, and 15,936 in the 2007–2011 cohort (data not shown). Among these, 557 used anti-TNF, 1144 were matched DMARD users and 656 matched non-users in 2002–2006; while, 690 used anti-TNF, 1651 were matched DMARD users and 532 matched non-users in 2007–2011 (Table 1). Among non-users, 81% used corticosteroid and/or NSAID in the follow-up during 2002–2006 compared to 74% during 2007–2011 (Appendix 3).

Patient baseline characteristics
Matching by high-dimensional propensity score, age and sex, removed most differences in baseline patient characteristics between the treatment groups except those related directly to the treatment choice such as prior corticosteroid and NSAID use, prior visits to rheumatologists and socioeconomic status (Table 2). In 2002–2006, patients in the anti-TNF group and those in the DMARD group had higher SES compared to non-users and were more likely than non-users to have taken corticosteroids and

### Table 1 Baseline characteristics of individuals with rheumatoid arthritis in Quebec in 2002–2006 and 2007–2011

| Variables                      | 2002–2006 |          | 2007–2011 |          |
|-------------------------------|-----------|----------|-----------|----------|
|                               | Anti-TNF  | DMARDs   | Non-users | Anti-TNF | DMARDs   | Non-users |
| Demographics                  |           |          |           |          |          |           |
| Age (mean ±SD) years          | 63.0(11.5)| 64.2(10.8)| 65.1(10.6)| 65.2(10.5)| 66.2(9.7)| 68.4(9.3) |
| Sex (female N(%))             | 426 (76.5)| 921 (80.5)| 562 (85.7)| 517 (74.9)| 1281 (77.6)| 426 (80.1) |
| Residence (urban N(%))        | 428 (76.8)| 899 (78.6)| 526 (80.2)| 531 (77.0)| 1316 (79.7)| 425 (79.9) |
| Higher income<sup>a</sup>      | 344 (61.8)| 691 (60.4)| 379 (57.8)| 417 (60.4)| 980 (59.4)| 339 (63.7) |
| Socioeconomic status N(%)     |           |          |           |          |          |           |
| Social quintile 0              | 58 (10.4)| 90 (7.9) | 48 (7.3)  | 49 (7.1)  | 100 (6.1) | 25 (4.7)   |
| Social quintile 1              | 106 (19.0)| 211 (18.4)| 88 (13.4)| 113 (16.4)| 285 (17.3)| 74 (13.9)  |
| Social quintile 2–3            | 192 (34.5)| 392 (34.3)| 238 (36.3)| 251 (36.5)| 618 (37.4)| 218 (41.0) |
| Social quintile 4–5            | 201 (36.1)| 451 (39.4)| 282 (43.0)| 276 (40.0)| 648 (39.2)| 215 (40.4) |
| Use of health services in prior year N(%) | | | | | | |
| Visit to rheumatologist        | 490 (88.0)| 946 (82.7)| 480 (73.2)| 608 (88.1)| 1365 (82.7)| 338 (63.5) |
| Comorbidity in prior year N(%) |           |          |           |          |          |           |
| Hematologic disorders          | 75 (13.5)| 112 (9.8)| 69 (10.5)| 72 (10.4)| 182 (11.0)| 69 (13.0)  |
| Heart failure                  | 16 (2.9) | 29 (2.5) | 9 (1.4)  | 19 (2.8) | 38 (2.3)  | 23 (4.3)   |
| Cerebrovascular disease        | 21 (3.8) | 23 (2.0) | 19 (2.9) | 10 (1.4) | 39 (2.4)  | 22 (4.1)   |
| Atrial fibrillation            | 14 (2.5) | 24 (2.1) | 13 (2.0) | 23 (3.3) | 54 (3.3)  | 18 (3.4)   |
| Ischemic heart disease         | 79 (14.2)| 138 (12.1)| 76 (11.6)| 65 (9.4) | 186 (11.3)| 56 (10.5)  |
| Peptic ulcer disease           | 7 (1.3)  | 10 (0.9) | 5 (0.8)  | 1 (0.1)  | 9 (0.5)   | 3 (0.6)    |
| Cancer                         | 39 (7.0) | 102 (8.9)| 51 (7.8) | 69 (10.0)| 172 (10.4)| 64 (12.0)  |
| Medication use in prior year N(%) | | | | | | |
| NSAIDs                         | 430 (77.2)| 843 (73.7)| 452 (68.9)| 435 (63.0)| 980 (59.4)| 248 (46.6) |
| Serotonin reuptake inhibitors  | 57 (10.2)| 107 (9.4)| 62 (9.5) | 71 (10.3)| 164 (9.9) | 532 (9.6)  |
| Gastroprotective agents        | 322 (57.8)| 664 (58.0)| 345 (52.6)| 463 (67.1)| 970 (58.8)| 328 (61.7) |
| Antidiabetics                  | 63 (11.3)| 115 (10.1)| 51 (7.8) | 81 (11.7)| 170 (10.3)| 77 (14.5)  |
| Corticosteroid                 | 414 (74.3)| 757 (66.2)| 400 (61.0)| 500 (72.5)| 928 (56.2)| 306 (57.5) |
| Anticoagulants                 | 27 (4.8) | 49 (4.3) | 31 (4.7) | 32 (4.6) | 106 (6.4) | 34 (6.4)   |
| Antihypertensives              | 294 (52.8)| 587 (51.3)| 305 (46.5)| 414 (60.0)| 944 (57.2)| 335 (63.0) |

<sup>a</sup>Those who do not receive any guaranteed income supplement
NSAIDs and to have visited a rheumatologist in the previous year. In 2007–2011, patients in the anti-TNF group were more likely than non-users to live in rural areas, to have received partial or total subsidies, to have used corticosteroid and NSAIDs and to have seen a rheumatologist in the previous year. They were also less likely to have CVD. In 2007–2011, patients in the DMARD group were more likely than non-users to have received partial or total subsidies, to have taken NSAIDs and visited a rheumatologist in the previous year. They were also less likely to have CHF and to have been using antidiabetics.

Hospitalizations for MSD-related events
The total number of patients who had MSD-related hospitalisations in 2002–2006 and 2007–2011 are displayed in Table 3. In 2002–2006, among the anti-TNF group, 39 individuals were hospitalized (crude rate 8.2/100 py), compared to 63 patients (6.4/100 py) among the DMARDs group and 53 patients (10.5/100 py) among the non-users group. While, in 2007–2011, 40 patients among the anti-TNF group were hospitalized for MSD-related events (6.8/100 py), compared to 70 patients (4.8/100 py) among the DMARDs group and 35 patients (8.6/100 py) among the non-user group. Figure 1 displays the Kaplan Meier curves of time to first MSD-related hospitalizations in the three treatment groups. In stratified multivariate Cox proportional hazard models, ischemic heart disease increased the risk of MSD-related hospitalizations in both periods. Use of antihypertensive agents in the previous year was negatively associated with MSD-related hospitalization in 2002–2006. Prior visits to rheumatologists were associated with a decreased risk of MSD-related hospitalizations in 2007–2011 (Table 4). In these models, the risk of MSD-related hospitalizations did not differ between anti-TNF users and non-users (0.95, 0.60, 1.50) in 2002–2006. The risk in that period tended to be lower in DMARD users 0.69 (0.46, 1.02). In 2007–2011, the risk in anti-TNF users tended to be lower than that in non-users,

### Table 2 Patient characteristics associated with anti-TNF and DMARD use: logistic regression model

| Variables                        | 2002–2006 |          | 2007–2011 |          |
|----------------------------------|-----------|----------|-----------|----------|
|                                  | OR (95 % CI) | OR (95 % CI) |
| Demographics                     |           |          |           |          |
| Residence (rural vs urbain)      | 1.21 (0.88, 1.66) | 1.05 (0.81, 1.38) | 1.43 (1.05, 1.96) | 1.15 (0.87, 1.51) |
| Higher income                    | 1.14 (0.90, 1.46) | 1.02 (0.83, 1.26) | 0.76 (0.59, 0.98) | 0.70 (0.56, 0.87) |
| Socioeconomic status             |           |          |           |          |
| Social quintile 0                | 1.02 (0.62, 1.68) | 0.75 (0.48, 1.17) | 1.33 (0.73, 2.41) | 1.00 (0.59, 1.71) |
| Social quintile 2–3 versus 1     | 0.69 (0.48, 0.98) | 0.69 (0.51, 0.93) | 0.71 (0.49, 1.01) | 0.72 (0.53, 0.98) |
| Social quintile 4–5 versus 1     | 0.61 (0.43, 0.88) | 0.66 (0.49, 0.90) | 0.82 (0.57, 1.18) | 0.74 (0.54, 1.01) |
| Use of health services in prior year |           |          |           |          |
| Visit to rheumatologist          | 2.73 (1.97, 3.79) | 1.74 (1.36, 2.22) | 4.41 (3.27, 5.95) | 2.86 (2.29, 3.60) |
| Comorbidity in prior year        |           |          |           |          |
| Hematologic disorders            | 1.32 (0.90, 1.94) | 0.92 (0.66, 1.28) | 0.88 (0.60, 1.30) | 0.96 (0.69, 1.32) |
| Heart failure                    | 1.97 (0.84, 4.61) | 1.95 (0.89, 4.29) | 0.82 (0.41, 1.63) | 0.52 (0.28, 0.94) |
| Cerebrovascular disease          | 1.43 (0.74, 2.75) | 0.75 (0.39, 1.42) | 0.38 (0.16, 0.86) | 0.63 (0.35, 1.14) |
| Ischemic heart disease           | 1.06 (0.72, 1.55) | 0.90 (0.64, 1.26) | 0.97 (0.63, 1.50) | 1.33 (0.93, 1.91) |
| Cancer                           | 0.86 (0.55, 1.35) | 1.17 (0.81, 1.69) | 0.82 (0.56, 1.20) | 0.88 (0.64, 1.22) |
| Medication use in prior year     |           |          |           |          |
| NSAIDs                           | 1.59 (1.21, 2.09) | 1.26 (1.02, 1.58) | 1.87 (1.46, 2.40) | 1.66 (1.35, 2.05) |
| Serotonin reuptake inhibitors     | 0.93 (0.62, 1.39) | 0.90 (0.65, 1.26) | 1.08 (0.72, 1.63) | 1.12 (0.79, 1.60) |
| Gastroprotective agents          | 1.04 (0.81, 1.33) | 1.18 (0.95, 1.45) | 1.09 (0.84, 1.42) | 0.85 (0.68, 1.06) |
| Antidiabetics                    | 1.39 (0.93, 2.08) | 1.28 (0.89, 1.83) | 0.76 (0.52, 1.09) | 0.71 (0.53, 0.97) |
| Corticosteroid                   | 1.87 (1.44, 2.43) | 1.22 (0.99, 1.50) | 1.92 (1.49, 2.47) | 0.96 (0.78, 1.18) |
| Anticoagulants                   | 0.90 (0.50, 1.62) | 0.84 (0.52, 1.37) | 0.98 (0.56, 1.71) | 1.39 (0.89, 2.19) |
| Antihypertensives                | 1.21 (0.94, 1.57) | 1.20 (0.97, 1.48) | 0.93 (0.72, 1.21) | 0.85 (0.68, 1.06) |
Table 3 Exposure duration, unadjusted rates and adjusted rate ratios (Cox proportional hazard models) of musculoskeletal hospitalizations in 2002–2006 and 2007–2011

| Exposure duration (days) | Hospitalization for musculoskeletal conditions | Hazard ratio (95 % CI) |
|--------------------------|-----------------------------------------------|------------------------|
|                          | Total Median (interquartile range) Number (unadjusted rate per 100 patient-yrs) |                        |
| 2002–2006                |                                             |                        |
| Anti-TNF                 | 174 128 365.0 (79.0) 39 (8.18) 0.95 (0.60, 1.50) |
| DMARDs                   | 358 954 365.0 (74.0) 63 (6.41) 0.69 (0.46, 1.02) |
| Non-user                 | 184 986 349.0 (173.0) 53 (10.46) 1.00 (Reference) |
| 2007–2011                |                                             |                        |
| Anti-TNF                 | 213 189 365.0 (102.0) 40 (6.85) 0.65 (0.37, 1.14) |
| DMARDs                   | 527 820 635.0 (54.0) 70 (4.84) 0.40 (0.24, 0.66) |
| Non-user                 | 148 381 349.5 (181.0) 35 (8.61) 1.00 (Reference) |

CI confidence interval

Fig. 1 Time to admission to the first hospitalization for a musculoskeletal condition: Kaplan Meier curves
although statistical significance was not reached (0.65; 0.37, 1.14). The risk in the DMARDs group was lower than that in non-users during this period (0.40; 0.24, 0.66).

**Secondary analyses**

Repeating the selection of cohorts and analyses among DMARDs users and non-users in 1998–2001, 2002–2006 and 2007–2011 revealed that in total, 3844 individuals used DMARDs and 7356 were matched non-users in 1998–2001; compared to 5978 DMARDs users and 11,439 matched non-users in 2002–2006; and 8260 DMARDs users and 15,361 matched non-users in 2007–2011. The total numbers of patients who were hospitalized for MSD-related events in the three periods are displayed in Table 5 by treatment group. In 1998–2001, the numbers of hospitalized patients (crude rate/100 py) were 229 (6.7/100 py) in the DMARD and 362 (6.6/100 py) in the non-user groups. While, in 2002–2006, they were 289 (5.4/100 py) in the DMARD and 614 (6.9/100 py) in the non-user groups; and in 2007–2011, they were 344 (4.5/100 py) in the DMARD and 797 (7.3/100 py) in the non-users groups. In multivariable Cox proportional Hazard models, the hazard ratios of MSD-related hospitalizations in the DMARD versus non-users groups were 1.16 (0.95, 1.41) in 1998–2001, 0.86 (0.73, 1.01) in 2002–2006 and 0.71 (0.60, 0.84) in 2007–2011.

**Discussion**

Our results suggests that in RA patients, the risks of MSD-related hospitalizations were similarly likely for those using anti-TNF therapy compared to non-users. The risk seemed higher in the first 5 years after the introduction of anti-TNF drugs to the market compared to the following 7–11 years. In DMARDs users that matched the anti-TNF users, MSD-related hospitalizations were less likely than in non-users in both periods, although results reached statistical significance in the second period. Analyses of all DMARD users revealed a similar risk among DMARD users compared to non-users in the period preceding the introduction of the anti-TNF to the market and a decreasing trend showing a lower risk among DMARD users in the following two periods. The apparently lower risk found in DMARD versus anti-TNF users is not surprising as anti-TNFs can only be prescribed in Quebec when DMARD therapy has failed. However, the higher risk of MSD-related hospitalizations among non-users is somehow concerning. The reasons for not using DMARDs or anti-TNF therapy during the study period among non-users was not known in our study. Further examination of the data revealed that the majority of non-users (81 % in 2002–2006 and 74 % in 2007–2011) used corticosteroid and/or NSAID in the follow-up. However, this alone cannot explain the higher hospitalization rate observed among non-users since the anti-TNF and DMARD groups also used these mediations in follow-up in similar to slightly higher proportions. In another published study, treatment discontinuation among RA patients reflected more the individual patient beliefs regarding treatment necessity and safety than the actual disease activity or route of drug administration [16].

---

**Table 4** Patients characteristics associated with hospitalization for musculoskeletal conditions: Cox proportional hazard models adjusted for treatment group at baseline

| Demographics     | 2002–2006 | 2007–2011 |
|------------------|-----------|-----------|
| Use of health services in prior year | - | 0.51 (0.30, 0.86) |
| Visit to Rheumatologist | - | 0.51 (0.30, 0.86) |
| Comorbidity in prior year | 2.34 (1.32, 4.13) | 2.69 (1.38, 5.22) |
| Ischemic heart disease | - | 0.71 (0.47, 1.08) |
| Medication use in prior year | - | 0.71 (0.47, 1.08) |

Also adjusted for patient characteristics listed in Table 2. Only significant associations are reported in this table.

**Table 5** Secondary analyses comparing Hospitalizations for musculoskeletal conditions among DMARDs users and non-users before and after the introduction of anti-TNF drugs to the Quebec market

| Exposure duration (days) | Number (Unadjusted rate per 100 patient-yrs) | Hazard ratio (95 % CI) |
|-------------------------|---------------------------------------------|-----------------------|
| Total Median (Quartile range) |
| 1998–2001 |
| DMARDs | 1,243,393 | 365.0 (12.0) | 229 (6.72) | 1.16 (0.95, 1.41) |
| Non-users | 1,998,164 | 317.0 (193.0) | 362 (6.61) | 1.00 (Reference) |
| 2002–2006 |
| DMARDs | 1,949,824 | 365.0 (0.0) | 289 (5.41) | 0.86 (0.73, 1.01) |
| Non-users | 3,270,739 | 365.0 (169.0) | 614 (6.85) | 1.00 (Reference) |
| 2007–2011 |
| DMARDs | 2,785,950 | 365.0 (0.0) | 344 (4.51) | 0.71 (0.60, 0.84) |
| Non-users | 3,970,012 | 296.0 (224.0) | 797 (7.33) | 1.00 (Reference) |

CI confidence interval
In a second study, about half of RA patients prescribed methotrexate interrupted their treatment within 1 year; these patients had higher disease activity compared to those who remained on treatment [17]. We also cannot rule out the possibility that anti-TNF use increased complication awareness which may have prompted physician contacts at the onset of symptoms and prevented deterioration requiring hospitalizations.

Few studies have considered admission to hospital as an effectiveness indicator of anti-TNF and DMARDs use. An Israeli study reported a decreased frequency of the number of all-cause hospitalizations during anti-TNF treatment compared to the period before treatment among patients with RA and spondyloarthopathies (44.2 versus 74.2 hospitalizations/100 py, p-value < 0.0001). The authors reported similar tendency related to hospitalizations due to exacerbation of the rheumatic disease (21.9 versus 47.5/100 py, p < 0.0001) and for orthopedic and surgical indications, however the latter analyses did not reach statistical significance [9]. A Japanese study reported no significant yearly difference in the prevalence of RA-related surgery after the introduction of anti-TNF drugs between 2004 and 2007, however a significantly higher proportion was observed for specific orthopedic surgery, starting in the second year. Among anti-TNF users, patients who had undergone RA-related surgery presented longer disease duration and higher functional disability compared to those who had not undergone this procedure [8]. Both of these studies were conducted shortly after the approval of anti-TNF drugs for the treatment of RA in their respective countries.

In our study, the decreasing trend of MSD-related hospitalizations found among DMARDs users over the three periods compared to the non-users perhaps, reflects the migration of the more severe cases from the DMARDs group after the approval of anti-TNF for reimbursement and over time.

Our study assessed the risk of MSD-related hospitalizations only. Hospitalizations for other reasons (including infections) are also important outcomes in RA patients, but were not within our study aim and were not investigated. Confounding by indication can greatly hinder the results of observational studies, because of the non-randomized nature of patient allocation to study treatments. The use of the propensity score methodology has been proposed to address this bias [18]. In our study, we used the high-dimensional propensity score to match patients in the treatment groups and create more balanced exposed and non-exposed groups [10]. In addition, we addressed selection bias in the design by constructing separate cohorts in two post-periods that separated the years immediately after the launch of the anti-TNF drugs (2002–2006) where channeling of more severe RA cases to anti-TNF treatment was very strong, from later years (2007–2011) where channeling remained but may have been less severe than that of earlier years [3, 5, 19–21].

**Conclusion**

In conclusion, the results of this population-based study suggest that the risk of MSD-related hospitalizations is lower in patients using DMARD alone versus those not using DMARD or anti-TNF therapy. The risk of MSD-related hospitalizations in those in whom DMARDs only has failed and are put on anti-TNF (with or without DMARDs) was similar to that of patients not using either of these therapies. Similar risks in patients not using DMARD or anti-TNF treatment to that of those using anti-TNF, presumably the more severe, indicate that some RA patients requiring treatment are not using one and are at risk of RA complications and perhaps disability.

**Appendix**

**Appendix 1**

Frequency of MSD disorders coded as principal diagnoses among study individuals hospitalized for MSD conditions.

| Table 6 Frequency of MSD disorders coded as principal diagnoses among study individuals hospitalized for MSD conditions |
|---------------------------------------------------------------|
| Diagnoses | 2002–2006 | 2007–2011 |
|---------------------------------------------------------------|
| All treatment groups | All treatment groups |
|---------------------------------------------------------------|
| Total number of patients hospitalized for MSD conditions | 155 | 145 |
| Diagnoses | N (%) | N (%) |
|---------------------------------------------------------------|
| Rheumatoid arthritis (ICD-9: 714; ICD-10: M05, M06) | 67 (43.23) | 37 (25.52) |
| Osteoarthrosis and allied disorders (ICD-9: 715; ICD-10: M16–M19) | 21 (13.55) | 51 (35.17) |
| Acquired deformities of joints (ICD-9: 717, 730, 733, 735, 736; ICD-10: M20-M24, M80, M84-87) | 29 (18.72) | 26 (17.93) |
| Other and unspecified disorders of back (ICD-9: 720–722, 724; ICD-10: M47, M48, M54) | 19 (12.27) | 8 (5.52) |
| Other disorders of synovium, tendon, and bursa (ICD-9: 726, 727, 728; ICD-10: M62, M65, M66, M70, M71, 75) | 9 (5.82) | 17 (8.35) |
| Other: ICD-9: 710, 716, 719, 729 ICD-10: M00, M13, M60, M72,M99 | 10 (6.46) | 6 (4.14) |
Appendix 2
Frequency of the primary diagnoses of MSD hospitalizations during the period 2007–2011 (ICD-10 codes, as recorded in the database, are listed in alphabetical order).

Table 7 Frequency of the primary diagnoses of MSD hospitalizations during the period 2007–2011 (ICD-10 codes, as recorded in the database, are listed in alphabetical order)

| Diagnosis                                                                 | N (%) |
|--------------------------------------------------------------------------|-------|
| Total number of patients hospitalized for MSD conditions during 2007–2011 | 145   |
| M0097; pyogenic arthritis, unspecified, ankle and foot                    | 1 (0.7) |
| M051, M053, M059 (rheumatoid lung disease, n = 1; rheumatoid arthritis with involvement of other organs, n = 3; seropositive rheumatoid arthritis, unspecified site, n = 2) | 6 (4.2) |
| M063, M068, M069 (rheumatoid nodules; n = 6; other specified rheumatoid arthritis, n = 1; rheumatoid arthritis, unspecified; n = 24) | 31 (21.4) |
| M1315, M1397 (monoathritis, pelvic region and thigh, n = 1; arthritis, unspecified, ankle and foot, n = 1) | 2 (1.4) |
| M167, M169 (coxa avascular, secondary, n = 2; unspecified, n = 9) | 11 (7.6) |
| M171, M179 (gonarthrosis, primary n = 5; unspecified, n = 28) | 33 (22.8) |
| M189; arthrosis of first carpometacarpal joint, unspecified | 2 (1.4) |
| M190, M199 (arthrosis, primary of other joints, n = 2; unspecified, n = 3) | 5 (3.5) |
| M201, M202, M204 (hallux valgus, n = 9; hallux rigidus, n = 2; other hammer toe(s) (acquired), n = 1) | 12 (8.3) |
| M218; other specified acquired deformities of limbs, forearm | 1 (0.7) |
| M224; chondromalacia patellae | 1 (0.7) |
| M2320; derangement of meniscus due to old tear or injury, multiple sites | 1 (0.7) |
| M2411; other articular cartilage disorders, shoulder region | 1 (0.7) |
| M2587; other specified joint disorders, ankle and foot | 1 (0.7) |
| M313; Wegener’s granulomatosis | 2 (1.4) |
| M4802, M4806, M4856 (spinal stenosis, cervical spine, n = 1; lumbar region, n = 3; collapsed vertebra, lumbar region, n = 1) | 5 (3.5) |
| M545; low back pain | 3 (2.1) |
| M6096; myositis, unspecified, lower leg | 1 (0.7) |
| M6227, M6289 (ischaemic infarction of muscle, ankle and foot, n = 1; other specified disorders of muscle, unspecified site, n = 1) | 2 (1.4) |
| M6593, M6589, M6596 (synovitis and tenosynovitis, forearm, n = 1; hand, n = 1; lower leg, n = 1) | 3 (2.1) |
| M6657; spontaneous rupture of unspecified tendon, ankle and foot | 1 (0.7) |
| M702; olecranon bursitis | 2 (1.4) |
| M703; other bursitis of elbow | 1 (0.7) |
| M7134, M7136, M7192 (other bursal cyst, hand, n = 2; lower leg, n = 1; bursopathy, unspecified, upper arm, n = 1) | 4 (2.8) |

Appendix 3
Use of NSAIDs and/or corticosteroids in follow-up. Descriptions of data: Frequency of MSD disorders coded as principal diagnoses among study individuals hospitalized for MSD conditions. Frequency of the primary diagnoses of MSD hospitalizations during the period 2007–2011 (ICD-10 codes, as recorded in the database, are listed in alphabetical order). Use of NSAIDs and/or corticosteroids in follow-up

Table 8 Use of NSAIDs and/or corticosteroids in follow-up

| Description | Anti-TNF | DMARDs | Non-users |
|-------------|----------|--------|-----------|
| Total number of patients | 2002–2006 | 557 | 1144 | 656 |
| NSAIDs in follow-up | 372 (66.8) | 788 (68.9) | 451 (68.8) |
| Corticosteroid in follow-up | 344 (61.8) | 650 (56.8) | 353 (53.8) |
| NSAIDs and/or corticosteroid in follow-up | 460 (82.6) | 959 (84.7) | 531 (80.9) |
| Total number of patients | 2007–2012 | 690 | 1651 | 532 |
| NSAIDs in follow-up | 389 (56.4) | 981 (59.4) | 257 (48.3) |
| Corticosteroid in follow-up | 413 (59.9) | 790 (47.8) | 276 (51.9) |
| NSAIDs and/or corticosteroid in follow-up | 568 (82.3) | 1251 (75.8) | 396 (74.4) |

Abbreviations
CHF, congestive heart failure; CVD, cerebrovascular disease; DMARDs, disease modifying antirheumatic drugs; ICD, Régie de l’assurance maladie du Québec; MSD, musculoskeletal; NSAIDs, Régie de l’assurance maladie du Québec; Py, patient-years; RA, Rheumatoid arthritis; RAMQ, Régie de l’assurance maladie du Québec; RCT, musculoskeletal; SD, standard deviation; SES, socioeconomic status; SSRI, serotonin reuptake inhibitors; TNF, Tumor Necrosis Factor

Funding
The study was supported by an unrestricted grant from Janssen Inc.
Availability of data and materials

The authors cannot share the original data for confidentiality agreement with the governmental agencies that hold the databases. The corresponding author will answer any question concerning these data upon request.

Author’s contributions

MAdÁM was involved in the design and analyses of the study. She also wrote the first draft of the manuscript and interpreted the results. SB and LB were involved in the study design, critical appraisal and interpretation of the results and manuscript revision. HN conducted all statistical analyses and revised the manuscript. ER was involved in all aspect of the study. She obtained funds and ethics approval to conduct the study. She obtained the administrative data and was involved in the study design. She supervised data analyses, critically appraised and interpreted the results and revised the manuscript. All authors approved the final version of the manuscript.

Competing interests

Elham Rahme has received grants and consulting fees from Janssen Inc. to support the study. She has also received grants and consulting fees from Pfizer Canada Inc. in the course of other unrelated studies. The sponsor was not involved in the design of the study or writing of the manuscript. Sasha Bernatsky, Louis Bessette and Marina A A Machado have not received any funds related to this study and have no conflict of interest to declare.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Permission to link the data was obtained from the Provincial Ethics Board. Approval to conduct the study was obtained from the McGill University Health Centre Ethics Review Board. The patient consent form is not applicable to this retrospective cohort study using health services administrative databases.

Author details

1Research Institute of the McGill University Health Centre, Montreal, QC, Canada. 2College of Medicine, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil. 3Department of Medicine, Division of Clinical Epidemiology, McGill University Health Centre, 687 Pine Ave West, V building, Montreal, QC H3A 1A1, Canada. 4Centre Hospitalier Universitaire de Québec, Laval University, Quebec City, QC, Canada.

Received: 1 March 2016 Accepted: 17 June 2016 Published online: 19 July 2016

References

1. Bykerk VP, Akhavan P, Hazlewood GS, Scheir O, Dooley A, Harasou B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. J Rheumatol. 2012;39(8):1559–82.
2. http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/medicaments/mme/medicaments/S8.pdf. RAMQ - Régie de l'assurance maladie du Québec. List of Medications. Accessed 12 Jan 2015.
3. Simard JF, Arkema EV, Sondstrom A, Géborek P, Savoie T, Béland LA, et al. Ten years with biologics: to whom do data on effectiveness and safety apply? Rheumatology (Oxford). 2011;50(1):204–13.
4. Aga AB, Lie E, Uhlig T, Olsen IC, Wierod A, Kalstad S, et al. Time trends in disease activity, response and remission rates in rheumatoid arthritis during the past decade: results from the NOR-DAMRD study 2000–2010. Ann Rheum Dis. 2015;74(2):381–8.
5. Soderlin MK, Geborek P. Changing pattern in the prescription of biological treatment in rheumatoid arthritis. A 7-year follow-up of 1839 patients in southern Sweden. Ann Rheum Dis. 2008;67(1):37–42.
6. Wiens A, Verison R, Corrier CJ, Otuki MT, Pontarolo R. Meta-analysis of the efficacy and safety of adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis. Pharmacotherapy. 2010;30(4):339–53.
7. Mosots RJ, Naidoo-Groot B. The efficacy of biologic agents in patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor inhibitors: a systematic review. Rheumatology (Oxford). 2012;51(12):2252–61.
8. Yasui T, Nishino J, Kadono Y, Matsui T, Nakamura K, Tanaka S, et al. Impact of biologics on the prevalence of orthopedic surgery in the National Database of Rheumatic Diseases in Japan. Mod Rheumatol. 2010;20(3):233–7.
9. Zisman D, Haddad A, Hashoul S, Laor A, Bitterman H, Rosner I, et al. Hospitalizations of patients treated with anti-tumor necrosis factor-alpha agents – a retrospective cohort analysis. J Rheumatol. 2013;40(1):16–22.
10. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Moggun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology. 2009;20(4):512–22.
11. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol. 1995;48(9):999–1009.
12. Barber C, Lalonde D, Fortin PR. Systematic review of validation studies of the use of administrative data to identify serious infections. Arthritis Care Res (Hoboken). 2013;65(8):1343–57.
13. Rassen JA DMH WSS. Pharmacoepidemiology Toolbox. Boston, MA. http://www.hdpharmacepi.org. Accessed 12 Jan 2015.
14. Schmitz N, Nitsa D, Galey G, Malla A, Wang J, Boyer R, et al. Association between neighborhood-level deprivation and disability in a community sample of people with diabetes. Diabetes Care. 2009;32(11):1998–2004.
15. Pampalon R, Hamel D, Gamache P, Raymond G. A deprivation index for health planning in Canada. Chronic Dis Can. 2009;29(4):178–91.
16. Morgan C, McBeth J, Coringley L, Watson K, Hynich KL, Symmons DP, et al. The influence of behavioural and psychological factors on medication adherence over time in rheumatoid arthritis patients: a study in the biologics era. Rheumatology (Oxford). 2015;54(10):1780–91.
17. Pasma A, Schenk CV, Timman R, Busschbach JJ, van den Berst BJ, Molenaar E, et al. Non-adherence to disease-modifying antirheumatic drugs is associated with higher disease activity in early arthritis patients in the first year of the disease. Arthritis Res Ther. 2015;17:261.
18. Wolfe F, Flowers N, Burke TA, Arguelles LM, Pettritt D. Increase in lifetime adverse drug reactions, service utilization, and disease severity among patients who will start COX-2 specific inhibitors: quantitative assessment of channeling bias and confounding by indication in 6689 patients with rheumatoid arthritis and osteoarthritis. J Rheumatol. 2002;29(5):1015–22.
19. Arkema EV, Neovius M, Juel-Jensen JK, Simard JF, van Vollenhoven RF. Is there a sex bias in prescribing anti-tumour necrosis factor medications to patients with rheumatoid arthritis? A nation-wide cross-sectional study. Ann Rheum Dis. 2012;71(7):1203–6.
20. Hetland ML, Lindegaard HM, Hansen A, Podenphant J, Unkerskov J, Ringsdal VS, et al. Do changes in prescription practice in patients with rheumatoid arthritis treated with biological agents affect treatment response and adherence to therapy? Results from the nationwide Danish DANBIO Registry. Ann Rheum Dis. 2008;67(7):1023–6.
21. Kivén TK, Heiberg, Lie E, Kaufmann C, Mikkelsen K, Nordvag BY, et al. A Norwegian DAMRD register: prescriptions of DMARDs and biological agents to patients with inflammatory rheumatic diseases. Clin Exp Rheumatol. 2005;23(S Suppl 39):S188–94.