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Outpatient Use of Antimicrobials in Patients With Rheumatoid Arthritis Before and After Treatment With Tumor Necrosis Factor Inhibitors: A Nationwide Retrospective Cohort Study

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Objective. The objective of this study was to investigate the effect of tumor necrosis factor α inhibitor (TNFi) initiation on the use of antimicrobials among biologic-naïve patients with rheumatoid arthritis (RA).

Methods. Information on all biologic-naïve patients with RA was extracted from ICEBIO, a nationwide registry. Each patient was matched on age, sex, and calendar time to five randomly selected individuals from the general population. All filled antimicrobial and glucocorticoid prescriptions in the 2 years before and after initiation of the first TNFi were extracted from the Prescription Medicines Register. Prescriptions were quantified by using the number of filled prescriptions (NP) and defined daily doses.

Results. We extracted information on 359 patients with RA and 1795 comparators. During the 24 months before initiating treatment with TNFi, patients with RA received more prescriptions for antimicrobials than their matched general population comparators (mean ± SD: 2.8 ± 3.4 vs 1.6 ± 2.7; $P < 0.001$). The 24-month mean NP for patients with RA increased to 3.5 ± 3.9 ($P < 0.001$) after initiating TNFi: antibiotics, 2.6 ± 3.2 to 3.2 ± 3.5 ($P < 0.001$); antivirals, 0.06 ± 0.5 to 0.16 ± 0.7 ($P = 0.004$); and antimycotics, 0.14 ± 0.5 to 0.22 ± 0.9 ($P = 0.06$). The 12-month mean NP was highest in the second year after TNFi initiation (1.9 ± 2.4). No association was found between NP and glucocorticoids, age, body mass index, or pre-TNFi Disease Activity Score 28-joint count and C-reactive protein.

Conclusion. Patients with RA on TNFi are more commonly treated for infections in the outpatient settings than previously reported. Patients are prescribed more antimicrobials in the 2 years preceding TNFi initiation than the general population, and this use further increases after initiation of TNFi. In contrast to what is reported for infections requiring hospitalization, outpatient antimicrobial use remained elevated for at least 2 years.

INTRODUCTION

Patients with rheumatoid arthritis (RA) have increased susceptibility to infections than the general population and have a twofold risk of developing severe infections compared with matched controls (1–5). Some risk can be attributed to the disease itself and some to immunosuppressive treatment. Interestingly, case–control studies have shown previous antibiotic prescriptions density to be an independent risk factor for developing RA and juvenile idiopathic arthritis (6,7).

Targeted biologic therapies introduced a new era in rheumatology. The first class of treatments, the tumor necrosis factor α inhibitors (TNFi), was introduced shortly before the turn of the century and is still the most used targeted biologic agents in rheumatology. Because of the vital role of tumor necrosis factor α in the immune response, there were concerns regarding the potential for increased risk of infections in patients treated with TNFi. An increased incidence of primary tuberculosis soon became apparent in this group, validating these concerns (8,9). A growing body

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SIGNIFICANCE & INNOVATIONS

How might this impact clinical practice or future developments?

- Outpatient-treated infections are more common than previously reported in patients with rheumatoid arthritis treated with tumor necrosis factor α inhibitor (TNFi).
- The use of antimicrobials increased after the initiation of TNFi and remained high for the 2 years of follow-up.
- Clinicians may want to consider this increased use of antimicrobials when selecting and discussing treatment options with patients.

of evidence shows an increased frequency of serious infections leading to hospitalization in patients treated with TNFi (10–16). In the Icelandic population, infections are registered as the third most common adverse effect of TNFi therapy, and they are responsible for 10% of treatment discontinuation in all rheumatic patients, regardless of disease (17). Thus, it is clear that infections are a significant cause of morbidity in patients on TNFi therapy.

In clinical trials, severe infections are defined as infections requiring hospitalization or intravenous antibiotics or those resulting in death. Over the last decade, our understanding of severe infections in patients treated with TNFi has markedly increased. However, there is less information available regarding infections that do not require hospitalization or emergency department visits. A recent study demonstrated that 95% of patients with RA with infections on non-TNFi biologic disease-modifying antirheumatic drugs (bDMARDs) were treated as outpatients (18). Although these infections are not considered severe, they can affect the quality of life of these patients. Prior studies based on patient-reported infections have associated TNFi with increased incidence of outpatient infections in patients with RA (19–22). However, outpatient use of antimicrobials (antibiotics, antivirals, and antimycotics) has not been studied in this patient population.

This nationwide retrospective cohort study compares antimicrobial use among patients with RA before and after starting their first TNFi treatment with that among comparators from the same population.

PATIENTS AND METHODS

Patients with inflammatory arthritides treated with bDMARDs in Iceland are required to be registered in ICEBIO, a nationwide registry. Currently, ICEBIO has information on more than 98% of these patients. The registry is based on DANBIO and contains comprehensive patient characteristics, along with disease activity scores and information on treatment (23). Entries are done near treatment initiation, at 6 months, and then annually. The present study includes all biologic-naïve patients with RA registered in ICEBIO who received their first treatment episode with a TNFi from January 2005 to December 2015. Each patient was matched on age, sex, and calendar time to five individuals from the general population, randomly selected from Registers Iceland, the official civil registry.

Outcomes. The primary study outcome measure was the number of antimicrobial prescriptions filled by an individual during a 2-year period. The Icelandic Directorate of Health operates the Icelandic Prescription Medicines Register (IPMR), which covers more than 95% of all filled drug prescriptions. From the IPMR, we extracted prescription data for antimicrobials taken orally for all individuals in the study for 2 years before and 2 years after initiating the first TNFi treatment. Each prescription contained information about the date the prescription was filled at the pharmacy, the code for the Anatomical Therapeutic Chemical Classification System (ATC), and the dose. All prescriptions for oral medications with ATC codes starting with J01 (antibiotics), J02 (antimycotics), J05 (antivirals), and H02AB (glucocorticoids) and with the ATC code P01AB01 (metronidazole, antibiotic) were included in the study. Prescriptions with ACT codes J04 (antimycobacterial), J05AR (anti-HIV), and J05AP (anti-hepatitis C) were excluded. Antimicrobial use was further quantified by defined daily doses (DDDs), as specified by the World Health Organization (WHO), at the time of data extraction in November 2019 (24). The WHO defines DDD for a medication as the average maintenance dose per day for its main indication in adults (24). That makes, for example, 1 DDD equal to a total daily dose of 500 mg of azithromycin, 1000 mg of ciprofloxacin, or 1500 mg of amoxicillin.

Covariates and stratification. In addition to age and sex, information on disease activity was extracted from ICEBIO at the start of TNFi therapy (baseline) and at month 18, including

Table 1. Baseline patient demographics of 359 patients with rheumatoid arthritis who started their first-line TNFi treatment

	Value
Total, N	359
Age (years), mean ± SD	52.9 ± 14.1
Female sex, n (%)	261 (72.7)
Years from diagnosis (n = 323), mean ± SD	8.2 ± 8.2
BMI (n = 216), mean ± SD	27.3 ± 5.2
Patients with prescription for oral glucocorticoids in the previous 2 years, n (%)	259 (72.1)
Smoking history, n (%)	
No data	125 (34.8)
Never	104 (29)
Previous	93 (25.9)
Current	37 (10.3)
TNFi type, n (%)	
Infliximab	170 (47.4)
Etanercept	119 (33.1)
Golimumab	38 (10.6)
Adalimumab	23 (6.4)
Infliximab biosimilars	9 (2.5)

Abbreviations: BMI, body mass index; TNFi, tumor necrosis factor α inhibitor.

Table 2. Disease activity at treatment start and after month 18 of treatment with TNFi

	Baseline	Month 18
VAS fatigue, mean ± SD (n)	64.6 ± 23.6 (251)	38.9 ± 26.6 (188)**
VAS pain, mean ± SD (n)	60.9 ± 23.7 (253)	34 ± 25.3 (188)**
VAS patient global, mean ± SD (n)	66.4 ± 22.2 (258)	36.52 ± 26 (198)**
VAS doctor global, mean ± SD (n)	57.5 ± 17 (259)	21.15 ± 16.1 (196)**
DAS28-CRP, mean ± SD (n)	4.8 ± 1.1 (252)	2.8 ± 1.1 (195)**
HAQ, mean ± SD (n)	1.2 ± 0.7 (253)	0.73 ± 0.7 (192)**

Abbreviations: DAS28-CRP, Disease Activity Score 28 for Rheumatoid Arthritis with C-reactive protein; HAQ, Health Assessment Questionnaire; TNFi, tumor necrosis factor α inhibitor; VAS, visual analog scale.
**$P < 0.001$ by paired *t*-test.

visual analog scales (VAS) for pain, fatigue, global health assessment, and physician global assessment; Health Assessment Questionnaire (HAQ) scores; body mass index (BMI); smoking history; and Disease Activity Score 28-joint count and C-reactive protein (DAS28-CRP). Prescription data for oral glucocorticoids were extracted from the IPMR. These variables were used for both stratified analyses by sex and to construct multivariable models.

Antimicrobial and glucocorticoid use was quantified on the basis of the number of filled prescriptions (NP) per individual and in DDDs, as specified by the WHO (24). These variables were compared before and after TNFi initiation and analyzed further on the basis of demographics and disease activity. The Wilcoxon rank sum test was used for comparisons because the data were not normally distributed. Predictors of antimicrobial use were estimated by using univariable and multivariable Poisson linear regression, with the NP following TNFi initiation as the dependent variable. Because of overdispersion, quasi Poisson regression was used to calculate the standard errors and *P* values of the model. A significance level of 0.05 was set. Two multivariable Poisson linear regression models were built to evaluate the association between TNFi therapy and antimicrobial use. The first model was constructed to evaluate the effect of pretreatment factors by using disease activity measures at the start of TNFi therapy as covariates in addition to age and sex. A second model was built to evaluate the effect of disease activity after the initiation of TNFi therapy by using disease activity measures obtained at month 18.

All data were anonymized before analysis. Statistical analysis was performed in RStudio (version 1.2.5019; R Project for Statistical Computing), and data manipulation was performed in Microsoft Excel (version 16.37; Microsoft Corporation). The study protocol was accepted by the National Bioethical Committee and the Data Protective Authority in Iceland (license: VSN-18-008).

RESULTS

Patients. On December 31, 2017, ICEBIO contained information on 952 individuals who had been treated with TNFi. Of these, 359 patients with RA had initiated their first-ever treatment with TNFi during the study period, and these patients were age- and sex-matched to 1795 comparators. The mean age ± SD was 52.9 ± 14.1 years, with 18% older than

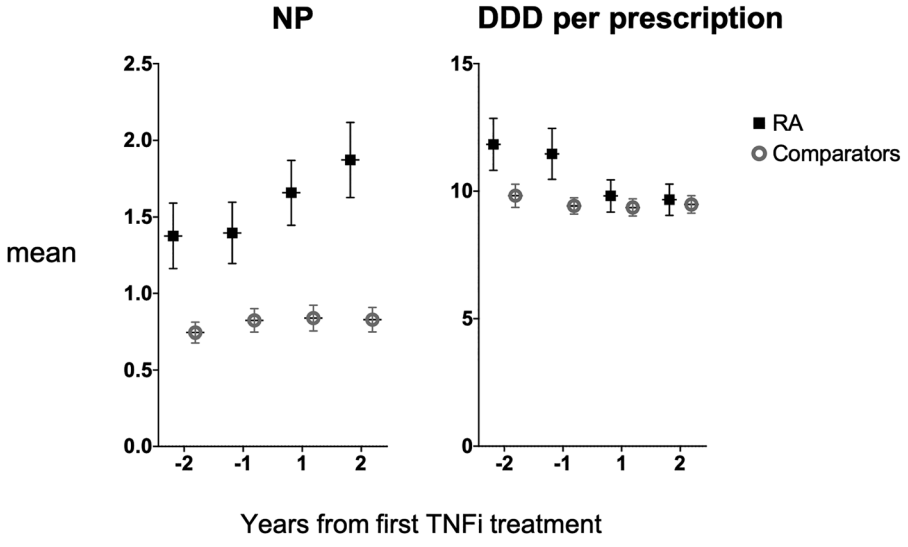

Figure 1. Mean yearly number of prescriptions (NP) of antimicrobials per individual and mean defined daily doses (DDDs) per prescription with 95% confidence intervals in the 2 years before and after tumor necrosis factor α inhibitor (TNFi) treatment in 359 patients with rheumatoid arthritis (RA) (black) and 1795 comparators (grey).

Table 3. Mean ± SD antimicrobial use as a number of prescriptions and defined daily dose per individual in the 2 years before and after TNFi therapy in a group of 359 patients with RA

	Number of prescriptions		Defined daily doses	
	RA (n = 359)	Comparators (n = 1795)	RA (n = 359)	Comparators (n = 1795)
Antibiotics				
Before TNFi	2.6 ± 3.2**	1.4 ± 2.5	31.6 ± 68.4	14.6 ± 34.9
After TNFi	3.2 ± 3.5**	1.5 ± 3	33 ± 57.3	15.2 ± 39.2
Antimycotic				
Before TNFi	0.14 ± 0.5	0.07 ± 0.5	0.3 ± 1.4*	0.18 ± 1.6
After TNFi	0.22 ± 0.9	0.06 ± 0.4	0.6 ± 3.4*	0.2 ± 2.3
Antiviral				
Before TNFi	0.06 ± 0.5*	0.06 ± 0.6	0.37 ± 3.4*	0.2 ± 2.6
After TNFi	0.16 ± 0.7*	0.07 ± 0.8	0.8 ± 4*	0.4 ± 4.6

Abbreviations: RA, rheumatoid arthritis; TNFi, tumor necrosis factor α inhibitor.
*$P < 0.05$; **$P < 0.001$ by Wilcoxon rank sum test.

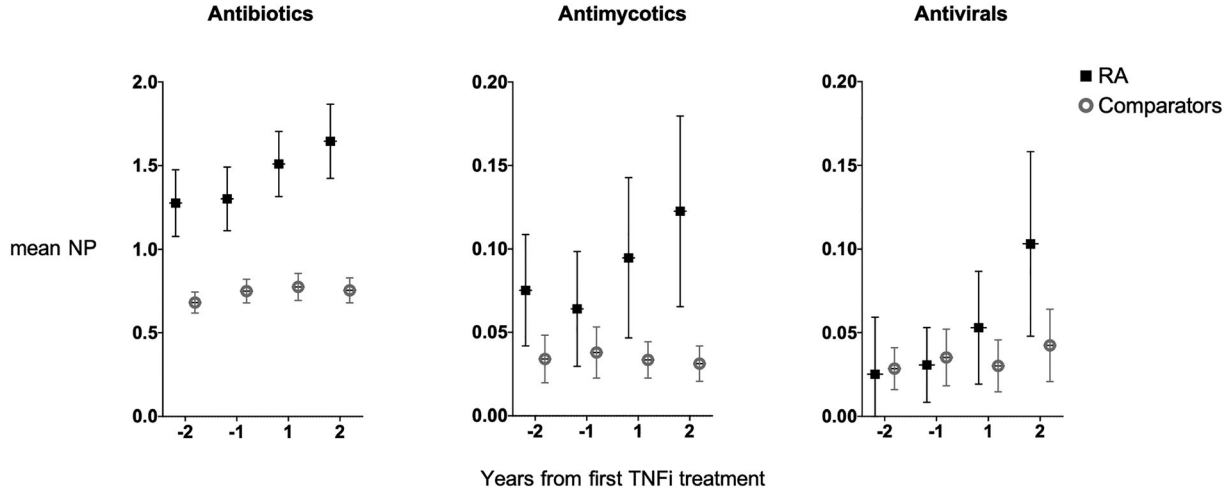

Figure 2. Mean yearly number of prescriptions (NP) and defined daily doses per prescription with 95% confidence intervals of antibiotics, antimycotics, and antivirals in the 2 years before and after tumor necrosis factor α inhibitor (TNFi) treatment in 359 patients with rheumatoid arthritis (RA) (black) and 1795 comparators (grey).

65 years of age. The most commonly used TNFi was infliximab (47%), followed by etanercept (33%), golimumab (9%), adalimumab (6%), and infliximab biosimilars (3%), as shown in Table 1. No patient received certolizumab pegol because it was not marketed in Iceland during the study period. The mean HAQ score at the initiation of TNFi was 1.2 ± 0.7, and the mean DAS28-CRP was 4.8 ± 1.1. Detailed disease activity scores are shown in Table 2.

Prescriptions. The patient group filled 2262 antimicrobial prescriptions. Of those, 2058 (91%) were for antibiotics, 128 (5.7%) were for antimycotics, and 76 (3.4%) were for antivirals. The comparator group filled 5287 antimicrobial prescriptions, of which 4811 (91%) were for antibiotics, 237 (4.5%) were for antimycotics, and 239 (4.5%) were for antivirals.

During the 2 years before initiating TNFi treatment, patients with RA filled more antimicrobial prescriptions than comparators (mean ± SD: 2.8 ± 3.4 vs 1.6 ± 2.7; $P < 0.001$) and received twice the DDDs (32.3 ± 68.6 vs 15.2 ± 30.3; $P < 0.001$), with a higher mean DDD per prescription (11.7 ± 11.5 vs 9.6 ± 7; $P < 0.001$), as illustrated in Figure 1.

Following TNFi therapy initiation, there was an increase in both the mean NP (2.8 ± 3.4 to 3.5 ± 3.9; $P < 0.001$) and the mean total DDDs (32.3 ± 68.6 to 34.4 ± 57.7; $P = 0.049$) in the RA group (Table 3). Conversely, the mean DDDs per prescription decreased (11.7 ± 11.5 to 9.7 ± 7.9; $P < 0.001$). Antimicrobial prescriptions did not decrease from the first to the second year of follow-up after TNFi treatment initiation, with a mean of 1.7 ± 2.0 prescriptions per year in the first year and 1.9 ± 2.4 prescriptions in the second year ($P = 0.102$). These annual means are shown in Figures 1 and 2. In a post hoc analysis evaluating prescriptions for each 6-month period after TNFi initiation, the patients with RA received the lowest mean NP in the first 6 months, and their use peaked between months 18 and 24 (0.81 ± 1.24 to 0.98 ± 1.52; $P = 0.048$).

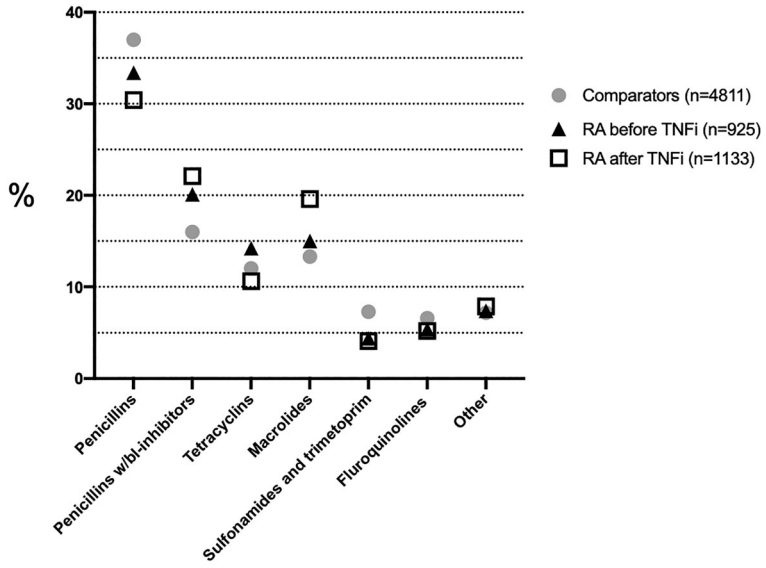

Figure 3. Distribution in percentages of the most commonly used antibiotics in patients with rheumatoid arthritis (RA) before (triangle, 925 prescriptions) and after (box, 1133 prescriptions) treatment with tumor necrosis factor α inhibitors (TNFi) and comparators (circle).

Table 4. Univariable and multivariable RR estimates at baseline and month 18 with 95% CIs

	Univariable RR	Multivariable RR at baseline (n = 244)	Multivariable RR at month 18 (n = 179)
Age (n = 359)	1.01 (1-1.01)	1 (0.99-1.01)	1 (0.99-1.01)
Sex (n = 355)			
Female (n = 261)	1 (reference)	1 (reference)	1 (reference)
Male (n = 94)	0.59 (0.43-0.78)**	0.73 (0.53-1)	0.77 (0.53-1.1)
BMI (n = 216)	1.01 (0.98-1.04)		
NP of antimicrobials before TNFi	1.1 (1.09-1.13)**	1.11 (1.09-1.14)**	1.1 (1.08-1.13)**
DAS28-CRP at baseline (n = 252)	1.1 (0.96-1.25)		
HAQ at baseline (n = 253)	1.37 (1.12-1.66)*	1.1 (0.89-1.34)	
VAS doctor at baseline (n = 259)	0.995 (0.99-1.00)		
VAS patient fatigue at baseline (n = 251)	1.01 (1-1.02)*	1 (0.99-1.01)	
VAS patient pain at baseline (n = 253)	1.01 (1-1.02)*	1 (0.99-1.01)	
VAS patient global at baseline (n = 258)	1.01 (1-1.02)*	1 (0.99-1.01)	
DAS28-CRP at month 18 (n = 195)	1.16 (1.02-1.32)*		0.91 (0.75-1.11)
HAQ at month 18 (n = 192)	1.36 (1.09-1.68)*		0.86 (0.62-1.17)
VAS doctor at month 18 (n = 196)	1.01 (1-1.02)*		1.01 (1-1.02)
VAS patient fatigue at month 18 (n = 188)	1.01 (1-1.02)*		1.01 (0.999-1.013)
VAS patient pain at month 18 (n = 188)	1.01 (0.99-1.01)		
VAS patient global at month 18 (n = 198)	1 (0.99-1.01)		
Smoking			
Never (n = 104)	1 (reference)		
Current (n = 36)	0.95 (0.62-1.42)		
Previous (n = 93)	1.18 (0.88-1.57)		
Treatment			
Infliximab and bs (n = 179)	1 (reference)		
Adalimumab (n = 23)	0.92 (0.54-1.47)		
Etanercept (n = 119)	1.13 (0.89-1.45)		
Golimumab (n = 38)	0.95 (0.63-1.39)		
NP of glucocorticoids before TNFi (n = 359)	1.01 (0.97-1.04)		
DDD of glucocorticoids before TNFi (n = 359)	1 (0.999-1)		
NP of glucocorticoids after TNFi (n = 359)	1.01 (0.99-1.03)		
DDD of glucocorticoids after TNFi (n = 359)	1 (0.99-1)		

Note: RR estimates with 95% CIs through quasi Poisson regression. Multivariate RRs are adjusted for age and significant parameters from univariate analysis. Two multivariate models are shown: one using baseline predictors at the time of TNFi initiation and the second using disease activity measures at 18 months after TNFi initiation.
Abbreviations: BMI, body mass index; bs, biosimilars; CI, confidence interval; DAS28-CRP, Disease Activity Score 28 for Rheumatoid Arthritis with C-reactive protein; DDD, defined daily doses; HAQ, Health Assessment Questionnaire; NP, number of prescriptions; RR, relative risk; TNFi, tumor necrosis factor α inhibitor; VAS, visual analog scale.
*$P < 0.05$; **$P < 0.001$.

Penicillin and its derivatives were the most commonly prescribed antibiotics (53%), as shown in Figure 3, whereas fluconazole represented 95% (n = 121) of all antimycotic prescriptions and valaciclovir represented 95% (n = 74) of all antiviral prescriptions in the patient group. The mean NP and mean DDDs for antibiotics, antimycotics, and antivirals are presented in Table 3.

Analysis by sex. Women received nearly twice the mean NP for antimicrobials compared with men, both before (3.2 ± 3.7 vs 1.7 ± 2.3; $P < 0.001$) and after (4.0 ± 4.0 vs 2.3 ± 3.1; $P < 0.001$) TNFi therapy (Supplementary Figure 1). The mean number of antimicrobial prescriptions increased significantly in both sexes (women, $P < 0.001$; men, $P = 0.02$) after TNFi. Women received a higher mean NP for antibiotics and antimycotics than men, both before (antibiotics, $P < 0.001$; antimycotics, $P = 0.0017$) and after (antibiotics, $P < 0.001$; antimycotics, $P = 0.008$) TNFi. Antibiotic use increased among women (2.9 ± 3.5 to 3.6 ± 3.7; $P = 0.006$), but the increase seen among men did not reach statistical significance (1.7 ± 2.3 to 2.1 ± 2.8; $P = 0.06$). The mean NP for antivirals increased among men (0.00 ± 0.00 to 0.16 ± 0.72; $P = 0.01$), whereas the increase was not statistically significant for women (0.08 ± 0.56 to 0.16 ± 0.75; $P = 0.08$). The mean NP for antimycotics did not significantly change with initiation of TNFi, neither for men (0.01 ± 0.10 to 0.06 ± 0.35; $P = 0.2$) nor for women (0.18 ± 0.61 to 0.28 ± 0.97; $P = 0.1$).

Predictors of antimicrobial prescriptions following TNFi. In the univariable analysis, prior antimicrobial prescriptions, baseline HAQ score, and VAS for patient fatigue, patient pain, and global health assessment were associated with increased risk of filling an antimicrobial prescription, whereas male sex was associated with reduced risk. At month 18, DAS28-CRP, VAS for doctor global assessment and patient fatigue, and HAQ score were positively associated with increased antimicrobial use. Neither steroid use, age, smoking, BMI, nor the type of TNFi used was associated with changes in antimicrobial use. In multivariable models adjusted for age and other significant covariates on the univariable analysis, only the number of prior antimicrobial prescriptions remained a statistically significant predictor of increased antimicrobial use after TNFi initiation, as shown in Table 4.

DISCUSSION

This study showed that the use of all classes of antimicrobials increased following TNFi treatment initiation in patients with RA. These patients already received nearly twice the number of antimicrobial prescriptions compared with matched population comparators before treatment with TNFi started. The increase in use was positively associated with the number of antimicrobial prescriptions filled before TNFi treatment, but there was no association with age, BMI, disease activity, smoking, or glucocorticoid prescriptions.

The present study suggests a higher infection rate than previously reported. We found that patients with RA had a crude incidence rate of 139 prescriptions per 100 patient-years before treatment with TNFi, which increased to 176 prescriptions per 100 patient-years after TNFi initiation. Previous studies have shown infection rates of 23 to 62 per 100 patient-years in patients with RA on TNFi (19–22). These previously reported infection rates are lower than that for our age- and sex-matched comparators, which was 75 prescriptions per 100 patient-years. The differences between these studies are likely due to differences in study design. Previous studies have been based on patient-reported infections to the treating physician at specialist rheumatology clinics. These studies have an inherent risk of underreporting milder infections and may not include infections treated at other centers or by a general practitioner. A recent Danish study used comparative methodology and reported 76 to 87 antibiotic prescriptions per 100 patient-years (ACT codes starting with J01) in patients with RA treated with non-TNFi biologics (18).

In contrast, the current study uses a nationwide prescription drug database that includes nearly all filled prescriptions in the country. During the study period, all oral antibiotics, antivirals, and antimycotics required a prescription, except a single fluconazole tablet for vaginal candidiasis. This results in comprehensive coverage of outpatient-treated infections. Iceland's reported antimicrobial use has been just above the average of the European Union countries for the last decade (25). Although antimicrobic prescription rates differ between countries, an antimicrobial prescription should be a valuable surrogate for an infective event in which a physician deems treatment indicated. Prescriptions can be given prophylactically and may not always signal an infective event.

We observed that the patients with RA receive a lower mean DDD per prescription after being treated with TNFi. This might result from a channeling bias caused by a change in prescription habits in which physicians have a lower threshold to prescribe antimicrobials for patients treated with TNFi. Furthermore, patients with RA undergoing TNFi treatment might be more likely to seek medical help, have more regular access to the health care system, and obtain antimicrobial prescriptions more easily. The increased NP and lower DDD per prescription could be explained by these patients being treated for milder infections than they would have before TNFi treatment or by patients seeking medical help earlier and therefore requiring a lower dose of antimicrobials for each infection event.

Prior studies have mainly compared the infection risk of patients with RA on bDMARDs with that of patients with RA on conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). In these comparisons, the difference in underlying patient characteristics must be considered. It has been hypothesized that patients with RA with a disease that requires treatment with bDMARDs might have a higher inherent predisposition to infections than other patients with RA. Therefore, the increased

risk of infection observed cannot solely be attributed to the bDMARDs (19). The present study addresses this issue by comparing outpatient-treated infections following TNFi initiation with that in the immediately preceding period in the same patient group.

The increased antimicrobial use observed in this study was not associated with higher disease activity in multivariable models at baseline or at 18 months. Furthermore, we found no association with the NP or prescribed DDDs of glucocorticoid steroids. Both high disease activity and steroid use have been associated with an increased risk of severe infections in patients with RA (14,20,26–30). The increased risk attributed to glucocorticoids has repeatedly been demonstrated in observational studies, especially when combined with TNFi (20,30). However, randomized controlled trials (RCTs) have not been conclusive, and a meta-analysis of RCTs showed a null association between infections and steroid use in patients with RA (30). Although it is uncertain why we did not observe these associations in our study, we must consider the possibility of different underlying pathomechanisms and risks factors behind severe infections that require hospitalization and milder infections treated in the outpatient setting.

The previous history of antimicrobial prescription was a risk factor for increased antimicrobial use following treatment with TNFi in this study. This is similar to what has been described in studies on severe infections in which it has been demonstrated that previous severe infection is a risk factor for further hospitalizations due to infections after TNFi treatment (10,14,16). Our results add to this by suggesting that a history of frequent antimicrobial prescriptions could indicate increased risk of outpatient infections when starting treatment with TNFi.

Treatment with TNFi, and to a lesser extent with csDMARDs, carries a small to moderate risk of severe infections resulting in hospitalization (10–14,28,31,32). This increased risk is particularly prominent in the first 6 to 12 months of TNFi therapy and decreases with time (10,14,26,32,33). This time-dependent reduced risk of severe infections has been attributed to better functional status and decreased disease activity and steroid use following treatment with TNFi (26). Our multivariable model did not associate disease activity or steroid use with changes in antimicrobial usage, and thus our data do not support this explanation. An alternative explanation is the "healthy drug survivor effect," in which individuals who experience severe infections on TNFi are more likely to discontinue the TNFi, leaving only those who tolerate TNFi without severe infections to be observed (26). It might be that milder infections were less likely to cause patients to stop treatment with TNFi, and therefore no healthy drug survivor effect was seen in this study of outpatient infections.

The strengths of this study are its nationwide design, the completeness of the Prescription Medicines Register, and the reliability of ICEBIO. Although we did not have data on comorbidities and the use of other csDMARDs to include in our models, it is important that the inclusion of steroid prescriptions allows us to exclude steroids as a significant confounder. A potential limitation to the generalizability of this study is the common use of infliximab, which may be less commonly prescribed in some other countries.

In conclusion, patients with RA use more antimicrobials than comparators in the 2 years preceding TNFi treatment, and their use is significantly increased in the 2 years following the initiation of TNFi treatment. In contrast to the previously described reduced frequency of serious infections 6 to 12 months after TNFi initiation, our data show a sustained increase in antibiotic prescriptions throughout a 2-year period. These data suggest that the need for outpatient antimicrobials increases with TNFi treatment and remains elevated, in contrast to a temporary increase in severe infections. Further studies are needed to understand if this continues over more extended periods and to understand the impact on the quality of life.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Love had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bjornsson, Gudbjornsson, Love.
Acquisition of data. Bjornsson, Gudbjornsson.
Analysis and interpretation of data. Bjornsson, Palsson, Kristjansson, Gunnarsson, Grondal, Gudbjornsson, Love.

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APPENDIX A: MEMBERS OF THE ICEBIO GROUP

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