The impact of first-line tumour necrosis factor inhibitor treatment on anti-infective use in patients with axial spondyloarthritis: a nationwide retrospective cohort study

H. Thorhallsdottir[1], A.H. Bjornsson[2,3,5], T.J. Love[2,4], B. Gudbjornsson[2,5], on behalf of ICEBIO

[1]Department of Medicine, Landspitali University Hospital of Iceland, Reykjavik; [2]School of Health Science, University of Iceland, Reykjavik, Iceland; [3]Department of Rheumatology, Skåne University Hospital, Lund, Sweden; [4]Department of Science, [5]Centre for Rheumatology Research, Landspitali University Hospital of Iceland, Reykjavík, Iceland.

Abstract

Objective

To investigate the use of anti-infective prescriptions (AIPs) in axial spondyloarthritis (axSpA) patients treated with tumour necrosis factor α inhibitors (TNFi) therapy and determine factors associated with increased risk of anti-infective use.

Methods

In this nationwide matched cohort study, we extracted information on all adult biologic-naive patients with axSpA initiating treatment with a TNFi in 2003-2018 from ICEBIO. Each patient was matched on age, sex, and calendar time to five individuals from the general population. AIPs were collected from nationwide registers two years before and after TNFi initiation. Prescription incidence rates (IR) were calculated, and multivariable analysis was conducted.

Results

The study identified data on 378 axSpA patients. The axSpA patients had higher IR per patient-year (py) of AIPs than comparators (1.12 (1.04–1.20) vs. 0.40 (0.38–0.42), p<0.001) before TNFi treatment. After TNFi initiation, the IR per py of AIP increased to 1.43 ((1.35–1.52), p<0.001), with a significant increase for antibiotics (1.04 (0.97–1.12) to 1.29 (1.21–1.38), p<0.001) and antivirals (0.03 (0.2–0.04) vs. 0.07 (0.06–0.1), p<0.001). Prior AIPs, female sex, and higher HAQ score were associated with increased AIPs after TNFi initiation, while age, smoking, and the use of glucocorticoids or methotrexate were not.

Conclusion

Filled AIPs among axSpA patients increased after TNFi initiation in contrast to what has been documented in prior studies on severe infections. This indicates an increase in non-severe infections or a lower threshold for AIPs among physicians after treatment initiation. Furthermore, axSpA patients were prescribed more AIPs before TNFi treatment compared to the general population, suggesting elevated baseline infection risk.

Key words

axial spondyloarthritis, infections, anti-infective, TNF-inhibitors, out-patients, nationwide

Hlin Thorhallsdottir, MD
Aron H. Bjornsson, MD
Thorvardur J. Love, MD, PhD
Bjorn Gudbjornsson, MD, PhD

Please address correspondence to:
Hlin Thorhalldsottir
Department of Medicine,
Landspitali University Hospital of Iceland,
Naustabryggja 31, íbúð 402,
101 Reykjavik, Iceland.

E-mail: hlinthorhallsdottir@gmail.com

Received on November 28, 2024; accepted in revised form on June 13, 2025.

Competing interests: none declared.

Introduction

Axial spondyloarthritis (axSpA) is a chronic rheumatic disease characterised by pain and stiffness in the axial skeleton. It is often associated with extraspinal features such as enthesitis, dactylitis, and synovitis (1, 2). In Iceland, the prevalence of ankylosing spondylitis (AS), usually considered the prototype of axSpA, is 0.13%, with a male-to-female ratio of little less than 2:1 (3).

First-line treatment for axSpA involves NSAIDs and physical therapy. For those who fail to respond, tumour necrosis factor α inhibitors (TNFi) are recommended as a second option (2, 4). The safety profile of TNFi in axSpA patients is mainly based on studies on rheumatoid arthritis (RA), where baseline infection risk is already high, and treatment with TNFi further increases that risk (5-7) As the efficacy of TNFi has been well established among axSpA patients, and given its prevalent use in this patient group, more data on infection risk based on axSpA patients is needed (4).

The fundamental pathogenesis of axSpA is not fully understood. Still, it is thought that together with environmental factors and genetics, dysregulation in different immune system factors, such as TNF-α, interleukin-17, and Th17 cells, can lead to a chronic inflammatory environment (8) This, alongside other factors such as chest immobility and joint pathogenesis, might contribute to increased baseline infection risk in axSpA patients (9).

In the past few years, a growing number of studies have not found evidence that the use of TNFi among axSpA patients increases the risk of serious infections, *i.e.* infections that require hospitalisation or intravenous (iv) antibiotics (10-16). However, a recent meta-analysis indicates that non-serious infections treated as outpatient are a common adverse event in randomised control trials (RCTs) among patients with axSpA treated with biological or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) (6). Few real-life observational studies on non-serious infections in this patient group have been conducted, and to our knowledge, none on outpatient anti-infective use (6).

In the present study, we compare rates of outpatient anti-infective use in patients diagnosed with axSpA nationwide before and after initiation of TNFi therapy. Furthermore, we compare the outpatient anti-infective use of these patients to a comparator group from the same population and time frame.

Methods

Data source

Data was collected from the Icelandic Registry of Biologic Treatment (ICEBIO). ICEBIO contains health and disease information about 98% of all patients in Iceland diagnosed with inflammatory arthritis receiving treatment with bDMARDs. The registry is based on DANBIO, a nationwide registry of biological therapies in Denmark (17, 18). Registration is done by a rheumatologist at treatment initiation and then annually. This study collected data from all biologic-naïve patients initiating treatment with TNFi from 2003 through 2018 with the following International Classification of Disease Version 10 (ICD-10) codes: M45.9, M46.1, M46.8, and M46.9.

Each patient was matched on age, sex, and calendar time to five individuals from the general population, randomly selected by Statistics Iceland, the main official institute providing statistics on the nation of Iceland (19).

Data on outpatient prescriptions for antibiotics, antivirals, antimycotics, glucocorticoids, and DMARDs was extracted from the Icelandic Prescription Medicines Registers (IPMR), which covers more than 95% of all filled drug prescriptions in Iceland (20). In Iceland, all anti-infective medications require a prescription from a physician. Therefore, no anti-infective drugs delivered over the counter were included in the present study.

Study design

This was a nationwide retrospective, observational cohort study on axSpA patients who received their first TNFi treatment within the study period. We defined treatment start as the date each patient received their first TNFi prescription. The patients were observed two years before and after the initia-

tion of the TNFi treatment or up to 30 days after treatment discontinuation. The comparators were observed for the same time as their matched patient. We further divided the post-treatment period into four six-month-long periods.

Data collected

The following covariates and baseline characteristics were extracted from ICEBIO: Patient ID, diagnostic codes, date of diagnosis, date of treatment start with TNFi, age, sex, smoking history, body max index (BMI) and information from clinical assessment tools at the start of therapy (baseline) and at month 18, including Health Assessment Questionnaire (HAQ), The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and The Bath Ankylosing Spondylitis Functional Index (BASFI). The following Anatomical Therapeutic Chemical Classification system (ATC) codes were collected from the IMPR: J01 (antibiotics), P01AB01 (metronidazole), J02 (antimycotics), J05 (antivirals), glucocorticoids (H02AB) and methotrexate (L04AX03 and L01BA0). Prescriptions with ACT codes J04 (antimycobacterial), J05AR (anti-HIV), and J05AP (anti-hepatitis C) were excluded. Anti-infective and glucocorticoid use was quantified into the number of filled prescriptions (NP) per individual and in defined daily doses (DDDs) as specified by the World Health Organisation (WHO), at the time of data extraction in October 2021.

Study outcomes

The primary outcome of this study was the incidence rate (IR) of anti-infective prescriptions (AIPs) filled by an individual during the observed period. Each collected prescription contained the date the prescription was filled at the pharmacy and the prescribed dose.

Statistical analysis

Descriptive statistics (mean, standard deviation, percentage) were used to summarise baseline characteristics and disease activity.

Using NP, incidence rate (IR) per patient-year (py) with a 95% confidence interval (CI) was calculated for AIPs in axSpA patients and comparators during the pre-and post-treatment period. Additionally, the Poisson exact test was used to calculate the incidence rate ratio (IRR) and its 95% CI for AIPs in axSpA patients during the post-treatment period and for comparators during the pre-treatment period relative to AIPs among axSpA patients in the pre-treatment period. The IRR with 95% CI was calculated for each subperiod within the post-treatment period relative to the first six months after treatment initiation among axSpA patients. Furthermore, we compared the overall means of DDDs from the observational period before and after TNFi initiation between axSpA patients and the comparator group. The Wilcoxon rank sum test was used as the data was not normally distributed. We also performed subgroup analysis to detect differences between sexes.

Poisson linear regression was used to determine factors associated with AIPs after TNFi initiation. Because of overdispersion in the data, Quasi-Poisson linear regression was used. A significance level of 0.05 was set. One univariable and two multivariable Poisson linear regression models were constructed. The first multivariable model was created to assess the effect of pre-treatment factors using baseline HAQ, age, and sex as predictive variables. The second model used demographic covariates and HAQ contained at month 18 after TNFi initiation as predictive variables. HAQ was selected over other clinical assessment tools due to having the most registrations.

There were no missing values for NP. If a patient did not receive any prescriptions during the study period, a value of 0 was recorded. For other variables included in the Poisson regression model, missing data were handled by excluding patients with incomplete information using a complete case analysis approach.

Data manipulation was performed in Microsoft Excel (v. 16.43). For the statistical analysis, RS Studio (v. 1.1.423) was used.

Table I. Baseline characteristics of 378 axSpA patients who started their first-line TNFi treatment.

	Value
Total, n	378
Age (years), mean ± SD	43 ± 13.1
Sex, n (%)	
Female	127 (33.6)
Male	251 (66.4)
Years from diagnosis, mean ± SD	7 ± 9.6
HAQ at baseline, mean ± SD (n)	0.87 ± 0.57 (297)
Smoking history, n (%)	
No data	102 (27)
Current	52 (13.8)
Never	157 (41.5)
Occasionally	8 (2.1)
Previously	59 (15.6)
BMI, mean ± SD	26.5 ± 3.97
Patient with prescription for oral glucocorticoids before TNFi, n (%)	111 (29.3)
Patients with prescription for MTX before TNFi, n (%)	91 (24.1)

axSpA: axial spondyloarthritis; TNFi: tumour necrosis factor α inhibitor; HAQ: Health Assessment Questionnaire; BMI: Body Mass Index; MTX: methotrexate.

Table II. Clinical assessment tools at treatment start and after 18 months of treatment.

	Baseline	Month 18
BASDAI, mean ± SD (n)	60.5 ± 17.9 (190)	29.5 ± 25.8 (175) ***
BASFI, mean ± SD (n)	45.7 ± 19.8 (170)	24.0 ± 22.9 (146) ***
HAQ, mean ± SD (n)	0.9 ± 0.6 (297)	0.4 ± 0.5 (244) ***

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; HAQ: Health Assessment Questionnaire; BASFI: Bath Ankylosing Spondylitis Functional Index.
*p<0.05; **p<0.01; ***p<0.001 by Wilcoxon rank sum test.

Table III. The incidence rate of prescriptions in axSpA patients before and after TNFi therapy and comparators.

	Number of prescriptions (NP)		Patient-years		Incidence rate, events/patient-years (95% CI)		Incidence rate ratio (95% CI)	
	axSpA	Comparators	axSpA	Comparators	axSpA	Comparators	axSpA	Comparators
Anti-infectives								
Before TNFi	834	1499	745.6	3724.2	1.12 (1.04-1.2)	0.4 (0.38-0.42)	Reference	0.36 (0.33-0.4)**
After TNFi	1030	1407	719.5	3593.3	1.43 (1.35-1.5)	0.4 (0.37-0.41)	1.27 (1.17-1.4)**	
Antibiotics								
Before TNFi	777	1338	745.6	3724.3	1.04 (0.97-1.12)	0.36 (0.34-0.37)	Reference	2.90 (2.65-3.17)**
After TNFi	928	1256	719.5	3593.3	1.29 (1.21-1.38)	0.35 (0.33-0.37)	1.23 (1.12-1.36)**	
Antivirals								
Before TNFi	19	86	745.6	3724.3	0.03 (0.2-0.04)	0.023 (0.02-0.03)	Reference	0.90 (0.55-1.58)
After TNFi	53	70	719.5	3593.3	0.07 (0.06-0.1)	0.02 (0.02-0.025)	2.89 (1.68-5.17)**	
Antimycotics								
Before TNFi	38	75	745.6	3724.3	0.05 (0.04-0.07)	0.02 (0.016-0.03)	Reference	0.40 (0.26 - 0.6)**
After TNFi	49	81	719.5	3593.3	0.07 (0.05-0.09)	0.02 (0.02-0.03)	1.33 (0.86- 2.10)	

axSpA: axial spondyloarthritis; TNFi: tumour necrosis factor α inhibitor; CI: confidence interval; NP: number of prescriptions; *p<0.01, **p<0.001.

Ethics statement

All data was anonymised before analysis. The National Bioethical Committee and the Data Protective Authority in Iceland approved the study protocol (VSN-18-008).

Results

Patients

Three hundred and seventy-eight patients met the diagnostic criteria of the study and underwent their initial treatment with TNFi within the study timeframe. The mean follow-up time per patient after TNFi initiation was 1.88 years. These patients were age- and sex-matched to 1886 comparators. The mean age was 43±13 years. Detailed baseline demographics of axSpA patients are shown in Table I. The mean values with SD (standard deviation) of clinical assessment tools at baseline and 18 months are presented in Table II.

Prescriptions

The patient group filled 1864 prescriptions during the observed period. Of those, 1705 (91.5%) were for antibiotics, 72 (3.9%) for antivirals, and 87 (4.7%) were for antimycotics. The comparator group filled 2906 prescriptions, of which 2594 (89%) were for antibiotics, 156 (5.3%) were for antivirals, and 156 (5.3%) were for antimycotics.

Detailed IRs per py of prescriptions and IRRs in axSpA patients and comparators before and after TNFi therapy are shown in Table III. The IR of AIPs in axSpA patients per py increased after TNFi initiation (1.12 (1.04–1.20) to 1.43 (1.35–1.52), p<0.001) (Fig. 1). The increase was significant for antibiotics (1.04 (0.97–1.12) to 1.29 (1.21–1.38), p<0.001), and antivirals (0.03 (0.2–0.04) to 0.07 (0.06–0.1), p<0.001)) but did not reach significance for antimycotics (Fig. 2).

When comparing axSpA patients and the comparator group before treatment, the axSpA group received higher IR per py for overall AIPs (1.12 (1.04–1.20)

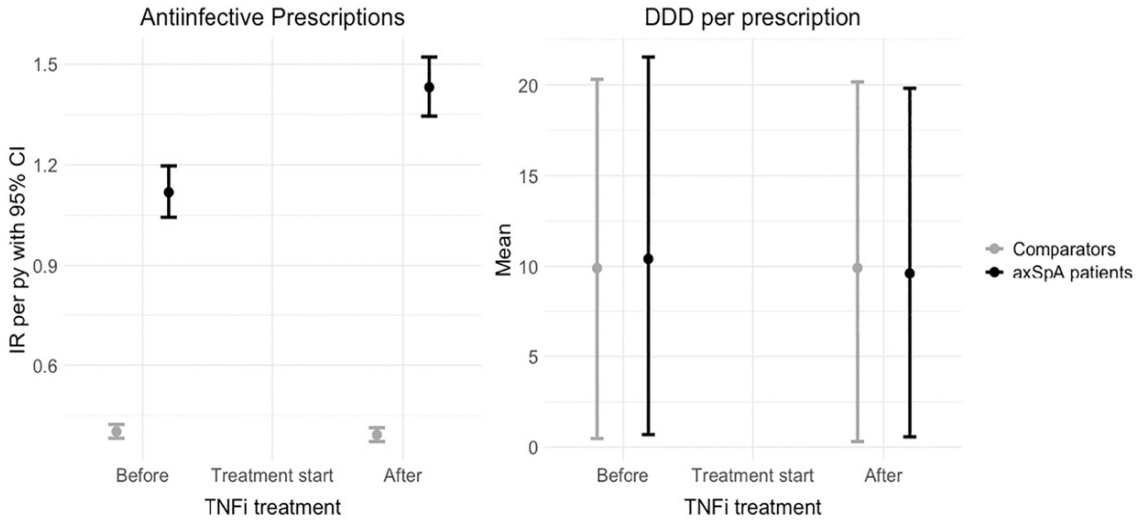

Fig. 1. Incidence rate (IR) for overall anti-infective prescriptions (AIPs) and mean defined daily dose (DDD) per AIP with 95% confidence interval (CI) before and after TNFi treatment in 378 patients with axial spondyloarthritis (axSpA) (black) and 1886 comparators (grey).

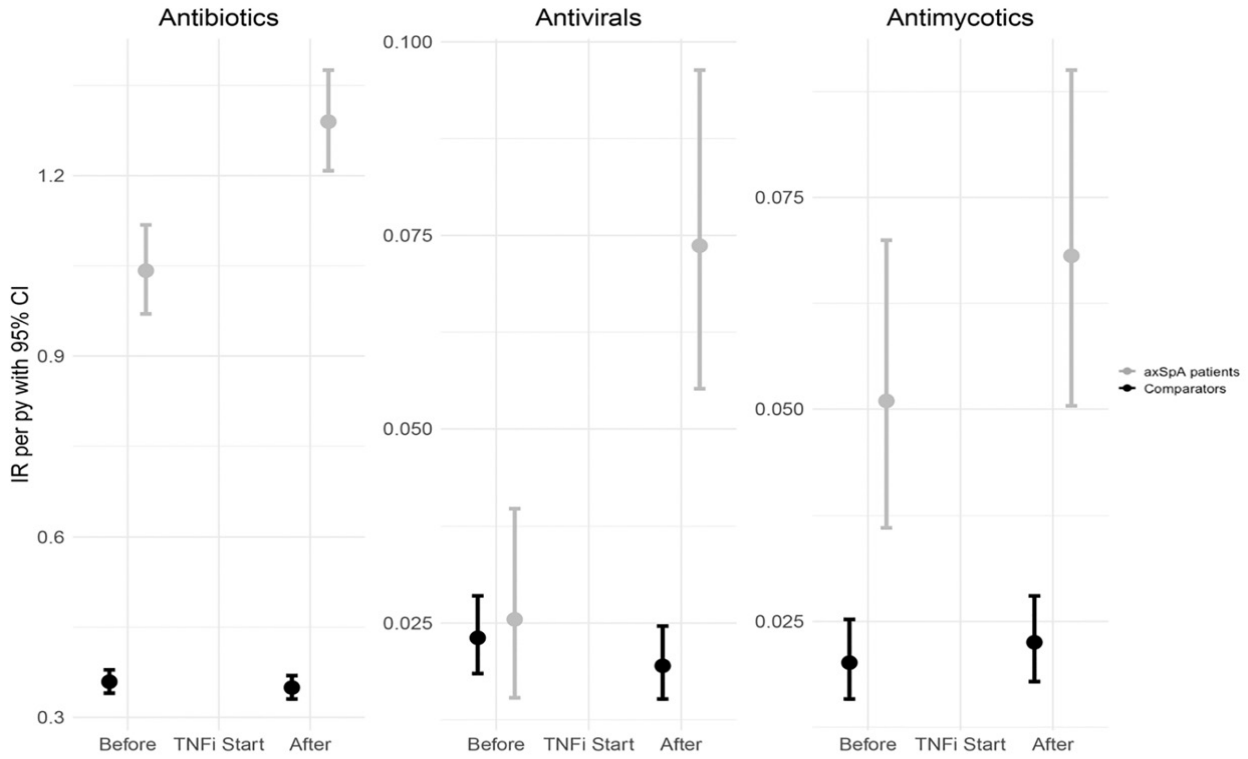

Fig. 2. Incidence rates (IR) with 95% confidence interval (CI) for antibiotic, antiviral and antimycotic prescriptions before and after TNFi treatment in 378 patients with axial spondyloarthritis (axSpA) (grey) and 1886 comparators (black).

vs. 0.40 (0.38–0.42), $p<0.001$) and in the antibiotics (1.04 (0.97–1.12) *vs*. 0.36 (0.34–0.37), $p<0.001$) and antimycotics (0.05 (0.04–0.07) *vs*. 0.02 (0.016–0.03), $p<0.001$) subcategories.

When comparing DDDs, there was a significant increase in the overall mean of DDDs for anti-infectives after TNFi initiation (25.7±60.2 to 28.7±56.3; $p<0.01$). However, the mean DDD per prescription of anti-infectives was stable (10.4±6.9 to 9.6±5.7, $p=1$) (Fig. 1).

When evaluating prescriptions for every six months after TNFi initiation, patients with axSpA only received significantly lower IR of antivirals in the first six months compared to after 24 months of treatment (0.05 (0.022–0.09) *vs*. 0.12 (0.07–0.18); $p<0.05$), other subcategories of anti-infectives did not show a significant difference (Fig. 3 and Supplementary Table S1).

Penicillin and its derivatives were the most commonly prescribed antibiotics before (36.2%, n=281) and after (37.4%, n=347) TNFi therapy among axSpA patients (Fig. 4). Among antivirals, valacyclovir was the most commonly prescribed before (89%, n=17) and after (89%, n=47) TNFi therapy, while fluconazole was the most commonly prescribed antimycotic before (79%, n=30) and after (94%, n=46) therapy.

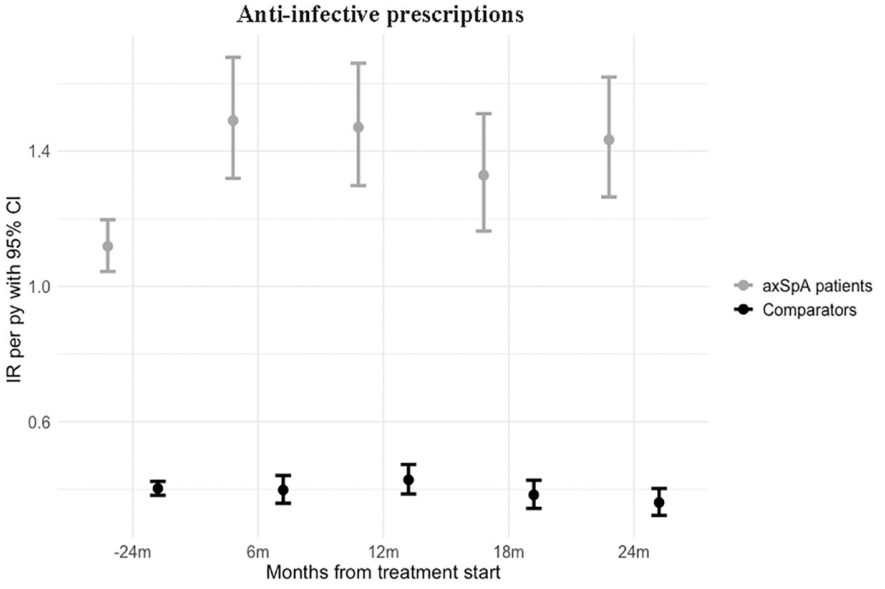

Fig. 3. Incidence rates (IR) of overall anti-infective prescriptions (AIPs) for each 6-month period before and after TNFi initiation among axSpA patients (grey) and comparators (black).

Analysis by sex

Subgroup analysis based on sex was conducted. Detailed IR and IRR of prescriptions in males *versus* females are shown in Supplementary Table S2. Overall, women had higher IR per py of AIPs than males before and after TNFi therapy and in every subcategory of anti-infectives, except for antivirals after TNFi therapy.

When comparing IRs before and after TNFi treatment, women had an increase

in overall AIPs (1.46 (1.32–1.62) to 1.88 (1.71–2.06); $p<0.001$) and antibiotics (1.33 (1.19–1.48) to 1.65 (1.5–1.83); $p<0.01$) while men had an increase in overall AIPs (0.94 (0.86–1.03) to 1.21 (1.1–1.31); $p<0.001$), antibiotics 0.90 (0.82–0.98) to 1.11 (1.02–1.21); $p<0.01$ and antivirals (0.01 (0.004–0.026) to 0.07 (0.06–0.1); $p<0.001$).

Predictors of AIPs following TNFi therapy

In the univariable analysis at baseline, the number of prior prescriptions of anti-infectives, elevated baseline HAQ score, and being a female were associated with an increased risk of filling later AIPs. At month 18, an elevated HAQ score was associated with an increased risk of AIPs. Neither age, smoking status, BMI, corticosteroids, nor MTX use was associated with changes in anti-infective use. In the multivariable model adjusting for significant covariates from the univariable baseline analysis and age, 297 patients were included. Prior prescriptions of anti-infectives, being a female, and elevated HAQ score remained significant risk factors for later AIPs. At month 18, 211 patients were included. Elevated HAQ score and prior anti-infective use were associated with a higher risk of AIPs. Detailed results from the regression models are shown in Table IV.

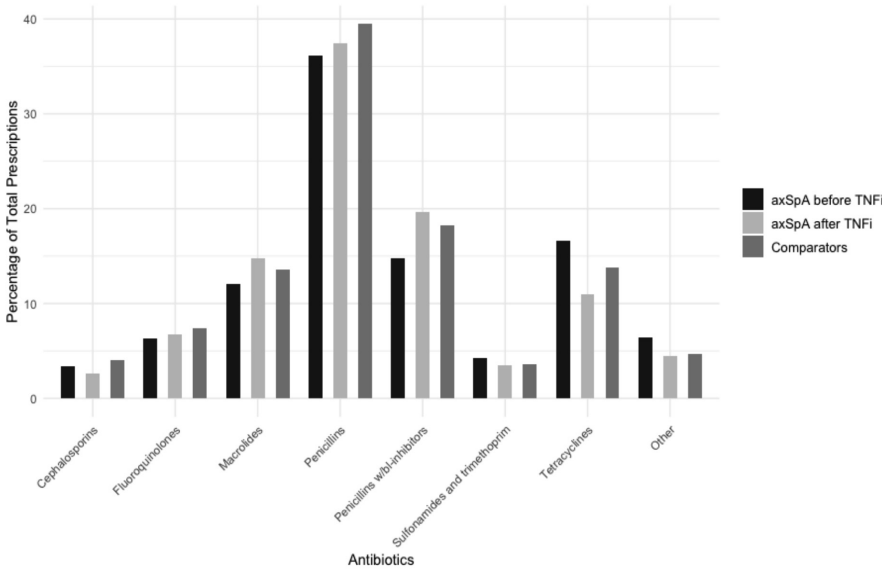

Fig. 4. Distribution in percentage of the most commonly used antibiotics among axSpA patients before (black) and after (grey) treatment with tumour necrosis factor α inhibitors (TNFi), and comparators (dark grey).

Table IV. Univariable RR and multivariable RR at baseline and 18 months with 95% CI.

	Univariable RR	Multivariable RR at baseline	Multivariable RR at month 18
Age	1.005 (0.995–1.01)	1.00 (1–1.01)	1.006 (0.99–1.01)
Sex			
Female	1.52 (1.18–1.94) **	1.27 (1.02–1.57) *	1.19 (0.94–1.51)
Male	1 (reference)	1 (reference)	1 (reference)
BMI	1.02 (0.98–1.07)		
NP anti-infectives before	1.10 (1.09–1.11) ***	1.09 (1.08–1.10) ***	1.08 (1.07–1.10) ***
HAQ at baseline	1.76 (1.15–1.82) ***	1.24 (1.03–1.49) *	
HAQ at month 18	1.76 (1.42–2.19) ***		1.31 (1.08–1.6) ***
Smoking			
Current	1 (reference)		
Never	0.88 (0.61–1.25)		
Occasionally	1.08 (0.48–2.41)		
Previous	0.79 (0.51–1.23)		
DDD of glucocorticoids before TNFi	1.00 (0.99–1.00)		
DDD of glucocorticoids after TNFi	1.001(0.99–1.00)		
MTX before TNFi			
Yes	0.80 (0.59–1.09)		
No	1 (reference)		
MTX after TNFi			
Yes	1.03 (0.78–1.36)		

RR, rate ratio; NP: number of filled prescriptions; TNFi: tumour necrosis factor α inhibitor; DDD: defined daily doses; HAQ: Health Assessment Questionnaire; MTX: methotrexate.
*$p<0.05$, **$p<0.01$, ***$p<0.001$.

Discussion

Our results showed a significant increase among axSpA patients in overall filled AIPs after initiation of TNFi treatment. The incidence rate of AIPs among our axSpA patients before TNFi therapy was 1.12 per py and 1.43 per py after TNFi initiation. Our matched comparators had much lower IR, or 0.40 per py. To our knowledge, no studies have been published on outpatient anti-infective use in axSpA patients on TNFi. Recent Icelandic study on RA patients reported higher IR of AIPs, or 1.39 per py before TNFi initiation and 1.76 per py after. Similar to our results, penicillin was their most commonly prescribed antibiotic (21).

Studies have not shown a significant increase in severe infections among axSpA patients after initiating TNFi therapy (10-16). However, recent meta-analyses on RCTs suggest a higher risk of common infections in axSpA on TNFi than on placebo (12, 22, 23). Our results align with these findings, indicating that although the risk of serious infections is low, a higher risk of non-serious infections is likely after TNFi initiation. Nonetheless, as our study is based on prescriptions, our results could also suggest a channelling bias, *i.e.* a lower threshold among physicians for AIPs after TNFi initiation. However, if that were solely the explanation, the possibility of lower DDDs per prescription might be expected, as has been seen in RA (21). That was not the case in our study.

Recently, a meta-analysis of RCTs and observational studies was conducted to estimate the incidence rate of non-serious infections in SpA patients (PsA and axSpA) on TNFi. The incidence rate was 0.7 per py for RCTs and 0.15 per py for observational studies. They concluded that this difference was likely due to recall bias in observational studies, where patients tend to underreport non-serious infections. In contrast, in RCTs, every adverse event is systematically recorded (6). The higher incidence rate seen in our study might be because of our study design. We used a prescription drug database that includes nearly all filled AIPs in Iceland, leading to the comprehensive inclusion of almost all outpatient infective events. This prevents recall bias and guarantees data is more reflective of a real-world population compared to data from RCTs (24). Another reason for the high incidence rate in our study might be the overprescription of anti-infectives in our cohort. However, Iceland's anti-infective use has been just above the average of the European Union countries in the recent decade, so we find this unlikely (25). As the first case of COVID19 in Iceland was diagnosed in February 2020, the possibility of increased AIPs for patients on TNFi during that year must be taken into account. However, study from Iceland reported that only 5 axSpA patients were diagnosed with COVID19 during the first wave from February to September in 2020, making it unlikely to significantly impact our results (26). Lastly, when comparing prescriptions and incidence rates, one must consider that prescriptions may not always represent an infective event as they can be given prophylactically.

Factors associated with increased anti-infective use were higher HAQ scores, prior anti-infective use and being a female. MTX was not associated with increased anti-infective use, aligning with previous studies on RA and SpA patients (16, 27). History of serious infections has been associated with later infections among axSpA patients, so our results suggest this also applies to common infections (15, 16, 27). Furthermore, our study adds to previous findings on RA patients where poor functional status is known to be a predictive factor for later infections (28).

Being a female has been linked to an increased risk of infection and antibiotic use in studies on axSpA patients before (16, 27, 29). This has mostly been attributed to a higher rate of urinary tract infections in women (16, 29). However, Frede et al. recently reported this difference between the genders in respiratory tract infections, suggesting other factors might be at play (27). Firstly, a growing body of immunological studies has identified differences between males and females with SpA (30-32). For example, higher levels of TNFα, iIL7A and Th17 have been reported in males, while females have been measured with elevated IL-6 (30, 31). Because IL-17A and TNF-α are known to affect inflammatory pathways leading to bone damage, it has been hypothesised that these differences cause men to more often present with severe radiographic changes (33, 34). It can be postulated that these differences in the immune response impact more than just the disease manifestation, *i.e.* comorbidities such as the host's susceptibility to infection. Secondly, women show a greater delay in diagnosis compared to men, likely due to atypical symptoms or less severe radiographic changes (32, 35). This delay can cause a worse disease burden, as reflected in higher disease activity scores, lower quality of life and poorer overall well-being in women (36, 37). Higher disease activity has been linked to an increased risk of infections, which might contribute to the gender differences in infection rates (29, 38). Lastly, studies show that women with SpA discontinue or switch TNFi treatments more often than men, possibly due to lower treatment response linked to higher body fat percentage (37, 39-41). This might lead to overtreatment with TNFis in women, explaining part of the difference in the gender infection risk. Clearly, further studies are needed on these differences in infection rates between males and females with axSpA.

Patients with axSpA had higher IR of anti-infectives than comparators before TNFi treatment. Based on results from prior RCTs, the infection rate in axSpA patients has generally been considered low (42). However, reported infection risk from RCTs should not be extrapolated to the public at large. Chung *et al*. recently conducted cohort studies comparing the risk of serious hospitalised infections in SpA patients to patients with non-specific back pain. They concluded that patients with SpA, not taking DMARDs, had an increased risk of some hospitalised infections (community-acquired pneumonia (CAP), urinary tract infection (UTI) and septic arthritis) (43, 44). Elevated baseline infection rate has repeatedly been demonstrated in patients with RA, where the disease's immunological dysfunction seems to impact patients' ability to fight infections (45, 46). Although the pathophysiology between these two diseases differs, axSpA is an inflammatory disorder where the immune system plays a vital role, possibly impacting patients' susceptibility to infections. However, the elevated infection rate among axSpA patients in our study could partly be explained by glucocorticoid and DMARD use before TNFi treatment; that said, glucocorticoid and MTX use was not associated with increased IR of anti-infectives in our multivariable analysis. Prior studies on axSpA patients, which have reported increased infection risk following glucocorticoid treatment, have all focused on serious infections (14, 15). Therefore, the possible difference in pathophysiology between serious and milder infections should be considered. Further studies on baseline infection risk in axSpA patients are needed.

The strength of this study was the retrospective nationwide design, which used ICEBIO and IPMR to allow for extensive, long-term data from across the country, increasing the generalisation of our results. However, the retrospective design is also a limitation due to inconsistencies in registered data, resulting in missing information on comorbidities and the ASDAS questionnaire. Meanwhile, the HAQ questionnaire, originally designed to assess functional status in RA patients, had the most registrations in our dataset. To minimise the impact of missing data, we opted to use the HAQ as a clinical

assessment tool instead of BASDAI or BASFI. Another possible limitation lies in the study design, as the AIPs is not matched to diagnostic codes. Therefore, we do not have information on the possible infection being treated.

In conclusion, our study shows that patients with axSpA received more AIPs than comparators before TNFi treatment, with prescriptions increasing after treatment initiation. Our results suggest a rise in non-serious infections after TNFi initiation in axSpA patients or a lower threshold among physicians for prescribing anti-infectives. Furthermore, our results indicate that the baseline infection risk of axSpA patients might be higher than previously thought, highlighting the need for further observational studies on the subject. Our study adds to a growing body of data on the safety profile of TNFi in axSpA patients. Our results will benefit clinicians in bringing awareness of the possible infection risk in this patient group.

Acknowledgements

We are grateful to all patients who regularly record their symptoms in ICEBIO and all rheumatologists in Iceland who are part of the ICEBIO group. We are also grateful to the Landspitali University Hospital Research Fund who supported the study. We also acknowledge Mrs Elinborg Stefánsdóttir, RN, for her assistance in the registration process of ICEBIO.

The ICEBIO group comprises K Erlendsson, AJ Geirsson, G Grondal, B Gudbjornsson, T Jonsdottir, H Jonsson, P Jonsson, TJ Love, BR Ludviksson, O Pallsson, GB Reynisdottir, S Saevarssdottir, K Steinsson, G Tomasson, and A Vikingsson.

References

1. WALSH JA, MAGREY M: Clinical manifestations and diagnosis of axial spondyloarthritis. *J Clin Rheumatol* 2021; 27(8): e547-60. https://doi.org/10.1097/rhu.0000000000001575
2. FATTORINI F, GENTILESCHI S, CIGOLINI C *et al*.: Axial spondyloarthritis: one year in review 2023. *Clin Exp Rheumatol* 2023; 41(11): 2142-50. https://doi.org/10.55563/clinexprheumatol/9fhz98
3. GEIRSSON AJ, EYJOLFSDOTTIR H, BJORNSDOTTIR G, KRISTJANSSON K, GUDBJORNSSON B: Prevalence and clinical characteristics of ankylosing spondylitis in Iceland - a nationwide study. *Clin Exp Rheumatol* 2010; 28(3): 333-40. https://doi.org/10.1056/nejmoa1001367
4. WARD MM, DEODHAR A, GENSLER LS *et al*.: 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Non-radiographic Axial Spondyloarthritis. *Arthritis Care Res* 2019; 71(10): 1285-99. https://doi.org/10.1002/acr.24025
5. LEOMBRUNO JP, EINARSON TR, KEYSTONE EC: The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheum Dis* 2009;68(7): 1136-45. https://doi.org/10.1136/ard.2008.091025
6. AUREAL M, SEAUVE M, LAPLANE S, LEGA J-C, CABRERA N, COURY F: Incidence of infections in patients with psoriatic arthritis and axial spondyloarthritis treated with biological or targeted disease-modifying agents: a systematic review and meta-analysis of randomised controlled trials, open-label studies and observational studies. *RMD Open* 2023; 9(3): e003064. https://doi.org/10.1136/rmdopen-2023-003064
7. GABRIEL SE, MICHAUD K: Epidemiological studies in incidence, prevalence, mortality, and comorbidity of the rheumatic diseases. *Arthritis Res Ther* 2009; 11(3): 229. https://doi.org/10.1186/ar2669
8. MAURO D, SIMONE D, BUCCI L, CICCIA F: Novel immune cell phenotypes in spondyloarthritis pathogenesis. *Semin Immunopathol* 2021; 43(2): 265-77. https://doi.org/10.1007/s00281-021-00837-0
9. YENDE S, ALVAREZ K, LOEHR L *et al*.: Epidemiology and long-term clinical and biologic risk factors for pneumonia in community-dwelling older Americans. *Chest* 2013; 144(3): 1008-17. https://doi.org/0.1378/chest.12-2818
10. MACHADO MA DE Á, BARBOSA MM, ALMEIDA AM *et al*.: Treatment of ankylosing spondylitis with TNF blockers: a meta-analysis. *Rheumatol Int* 2013; 33(9): 2199-213. https://doi.org/10.1007/s00296-013-2772-6
11. XU Z, XU P, FAN W *et al*.: Risk of infection in patients with spondyloarthritis and ankylosing spondylitis receiving antitumor necrosis factor therapy: A meta-analysis of randomized controlled trials. *Exp Ther Med* 2017; 14(4): 3491-500. https://doi.org/10.3892/etm.2017.5003
12. FENG H, ZHAO Y, KUANG W, DAI Y, CEN X, QIN F: Adverse events of tumor necrosis factor alpha inhibitors for the treatment of ankylosing spondylitis: A meta-analysis of randomized, placebo-controlled trials. *Front Pharmacol* 2023; 14: 1084614. https://doi.org/10.3389/fphar.2023.1084614
13. HOU L-Q, JIANG G-X, CHEN Y-F *et al*.: The comparative safety of TNF inhibitors in ankylosing spondylitis-a meta-analysis update of 14 randomized controlled trials. *Clin Rev Allergy Immunol* 2018; 54(2): 234-43. https://doi.org/10.1007/s12016-017-8623-6
14. WALLIS D, THAVANESWARAN A, HAROON N, AYEARST R, INMAN RD: Tumour necrosis factor inhibitor therapy and infection risk in axial spondyloarthritis: results from a longitudinal observational cohort. *Rheumatology* (Oxford) 2015; 54(1): 152-56. https://doi.org/10.1093/rheumatology/keu255
15. KOO BS, LIM Y-C, LEE M-Y *et al*.: The risk factors and incidence of major infectious diseases in patients with ankylosing spondylitis receiving tumor necrosis factor inhibitors. *Mod Rheumatol* 2021; 31(6): 1192-201. https://doi.org/10.1080/14397595.2021.1878985
16. MOURA CS, RAHME E, MAKSYMOWYCH WP, ABRAHAMOWICZ M, BESSETTE L, BERNATSKY S: Use of disease-modifying anti-rheumatic or anti-tumour necrosis factor drugs and risk of hospitalized infection in ankylosing spondylitis. *Scand J Rheumatol* 2019; 48(2): 121-27. https://doi.org/10.1080/03009742.2018.1470253
17. IBFELT EH, JENSEN DV, HETLAND ML: The Danish nationwide clinical register for patients with rheumatoid arthritis: DANBIO. *Clin Epidemiol* 2016; 8: 737-42. https://doi.org/10.2147/CLEP.S99490
18. RUNARSDOTTIR EE, GUNNARSDOTTIR AI, LOVE TJ, GUNNARSSON PS, GUDBJORNSSON B, ICEBIO: The majority of patients with psoriatic arthritis are not eligible for randomised clinical trials. *Clin Exp Rheumatol* 2018; 36(6): 1068-73. https://doi.org/10.1056/nejmoa1711335
19. [Internet]. Mannfjöldi eftir fæðingarlandi, kyni og aldri 1. janúar 1998-2024. PxWeb [cited 2024 Jun 24]. Available from: https://px.hagstofa.is/pxis/pxweb/is/Ibuar/Ibuar__mannfjoldi__3_bakgrunnur__Faedingarland/MAN12103.px/table/tableViewLayout2/
20. GUÐMUNDSSON LS, EINARSSON ÓB, JOHANNSSON M: Icelandic Medicines Registry (IMR). *In*: STURKENBOOM M, SCHINK T (Eds) Databases for Pharmacoepidemiological Research. 2021. Springer Series on Epidemiology and Public Health. https://doi.org/10.1007/978-3-030-51455-6_17
21. BJORNSSON AH, PALSSON O, KRISTJANSSON M *et al*.: Outpatient use of antimicrobials in patients with rheumatoid arthritis before and after treatment with tumor necrosis factor inhibitors: a nationwide retrospective cohort study. *ACR Open Rheumatol* 2021; 4(2): 187-94. https://doi.org/10.1002/acr2.11382
22. HU L, MAN S, JI X *et al*.: Risk of infections of biological and targeted drugs in patients with spondyloarthritis: meta-analysis of randomized clinical trials. *Chin Med J* (Engl) 2022; 135(8): 911-19. https://doi.org/10.1097/cm9.0000000000001928
23. SÉAUVE M, AURÉAL M, LAPLANE S, LEGA J-C, CABRERA N, COURY F: Risk of infections in psoriatic arthritis or axial spondyloarthritis patients treated with targeted therapies: a meta-analysis of randomized controlled trials. *Joint Bone Spine* 2024; 91(3): 105673. https://doi.org/10.1016/j.jbspin.2023.105673
24. PALSSON O, LOVE TJ, GUNNARSDOTTIR AI *et al*.: Patients with psoriatic arthritis who are not eligible for randomised controlled trials for TNF inhibitors have treatment response and drug survival similar to those who are eligible. *RMD Open* 2019; 5(2): e000984. https://doi.org/10.1136/rmdopen-2019-000984
25. [Internet]. 2021 Nov 18. Antimicrobial

consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report for 2020 [cited 2024 Aug 27]. Available from: https://www.ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-consumption-europe-2020
26. BJORNSSON AH, GRONDAL G, KRISTJANSSON M, JONSDOTTIR T, LOVE TJ, GUDBJORNSSON B: Prevalence, admission rates and hypoxia due to COVID-19 in patients with rheumatic disorders treated with targeted synthetic or biologic disease modifying antirheumatic drugs or methotrexate: a nationwide study from Iceland. *Ann Rheum Dis* 2021; 80(5): 671-72. https://doi.org/10.1136/annrheumdis-2020-219564
27. FREDE N, RIEGER E, LORENZETTI R *et al*.: Respiratory tract infections and risk factors for infection in a cohort of 330 patients with axial spondyloarthritis or psoriatic arthritis. *Front Immunol* 2022; 13: 1040725. https://doi.org/10.3389/fimmu.2022.1040725
28. WEAVER A, TROUM O, HOOPER M *et al*.: Rheumatoid arthritis disease activity and disability affect the risk of serious infection events in RADIUS 1. *J Rheumatol* 2013; 40(8): 1275-81. https://doi.org/10.3899/jrheum.121288
29. GERMANO V, CATTARUZZA MS, OSBORN *et al*.: Infection risk in rheumatoid arthritis and spondyloarthropathy patients under treatment with DMARDs, corticosteroids and TNF-α antagonists. *J Transl Med* 2014; 12: 77. https://doi.org/10.1186/1479-5876-12-77
30. GRACEY E, YAO Y, GREEN B *et al*.: Sexual dimorphism in the Th17 signature of ankylosing spondylitis. *Arthritis Rheumatol* 2016; 68(3): 679-89. https://doi.org/10.1002/art.39464
31. HUANG W-N, TSO TK, KUO Y-C, TSAY GJ: Distinct impacts of syndesmophyte formation on male and female patients with ankylosing spondylitis. *Int J Rheum Dis* 2012; 15(2): 163-68. https://doi.org/10.1111/j.1756-185x.2011.01687.x
32. WRIGHT GC, KAINE J, DEODHAR A: Understanding differences between men and women with axial spondyloarthritis. *Semin Arthritis Rheum* 2020; 50(4): 687-94. https://doi.org/10.1016/j.semarthrit.2020.05.005
33. ANDREASEN RA, KRISTENSEN LE, EGSTRUP K *et al*.: The impact of sex and disease classification on patient-reported outcome measures in axial spondyloarthritis: a descriptive prospective cross-sectional study. *Arthritis Res Ther* 2019; 21(1): 221. https://doi.org/10.1186/s13075-019-2012-x
34. MIOSSEC P: Update on interleukin-17: a role in the pathogenesis of inflammatory arthritis and implication for clinical practice. *RMD Open* 2017; 3(1): e000284. https://doi.org/10.1136/rmdopen-2016-000284
35. JOVANÍ V, BLASCO-BLASCO M, RUIZ-CANTERO MT, PASCUAL E: Understanding how the diagnostic delay of spondyloarthritis differs between women and men: a systematic review and metaanalysis. J *Rheumatol* 2017; 44(2): 174-83. https://doi.org/10.3899/jrheum.160825
36. TOURNADRE A, PEREIRA B, LHOSTE A *et al*.: Differences between women and men with recent-onset axial spondyloarthritis: results from a prospective multicenter French cohort. *Arthritis Care Res* 2013; 65(9):1482-89. https://doi.org/10.1002/acr.22001
37. RUSMAN T, VAN VOLLENHOVEN RF, VAN DER HORST-BRUINSMA IE: Gender differences in axial spondyloarthritis: women are not so lucky. *Curr Rheumatol Rep* 2018; 20(6): 35. https://doi.org/10.1007/s11926-018-0744-2
38. AU K, REED G, CURTIS JR *et al*.: High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2011; 70(5): 785-91. https://doi.org/10.1136/ard.2010.128637
39. ARENDS S, BROUWER E, VAN DER VEER E *et al*.: Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther* 2011; 13(3): R94. https://doi.org/10.1186/ar3369
40. LUBRANO E, PERROTTA FM, MANARA M *et al*.: The sex influence on response to tumor necrosis factor-α inhibitors and remission in axial spondyloarthritis. *J Rheumatol* 2018; 45(2): 195-201. https://doi.org/10.3899/jrheum.170666
41. MICHEROLI R, HEBEISEN M, WILDI LM *et al*.: Impact of obesity on the response to tumor necrosis factor inhibitors in axial spondyloarthritis. *Arthritis Res Ther* 2017; 19(1): 164. https://doi.org/10.1186/s13075-017-1372-3
42. FOUQUE-AUBERT A, JETTE-PAULIN L, COMBESCURE C, BASCH A, TEBIB J, GOSSEC L: Serious infections in patients with ankylosing spondylitis with and without TNF blockers: a systematic review and meta-analysis of randomised placebo-controlled trials. *Ann Rheum Dis* 2010; 69(10): 1756-61. https://doi.org/10.1136/ard.2008.098822
43. CHUNG HY, CHAN SCW, SUN FSK: Risk of nonpulmonary infections requiring hospitalization in spondyloarthritis. *Immun Inflamm Dis* 2022; 10(5): e615. https://doi.org/10.1002/iid3.615
44. CHUNG HY, TAM LS, CHAN SCW *et al*.: Risk of community-acquired pneumonia requiring hospitalization in patients with spondyloarthritis. *Ther Adv Musculoskelet Dis* 2020; 12: 1759720X20962618. https://doi.org/10.1177/1759720X20962618
45. DORAN MF, CROWSON CS, POND GR, O'FALLON WM, GABRIEL SE: Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. *Arthritis Rheum* 2002; 46(9): 2287-93. https://doi.org/10.1002/art.10524
46. MUTRU O, LAAKSO M, ISOMÄKI H, KOOTA K: Ten year mortality and causes of death in patients with rheumatoid arthritis. *Br Med J Clin Res Ed* 1985; 290(6484): 1797-99. https://doi.org/10.1136/bmj.290.6484.1797
47. WINTHROP KL: Infections and biologic therapy in rheumatoid arthritis: our changing understanding of risk and prevention. *Rheum Dis Clin North Am* 2012; 38(4): 727-45. https://doi.org/10.1016/j.rdc.2012.08.019