Temporal trends in overall infection incidence in patients with inflammatory arthritides treated with tumour necrosis factor inhibitors: a nationwide cohort study

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Abstract

Objective

To investigate temporal trends in infection rates among patients with inflammatory arthritides receiving tumour necrosis factor inhibitors (TNFi) and explore whether the incidence of infections among patients starting TNFi treatment has changed with increasing access to TNFi.

Methods

In this nationwide matched cohort study, we extracted information on all adult biologic-naive patients with rheumatoid arthritis, psoriatic arthritis, and spondyloarthritides initiating treatment with a TNFi from the ICEBIO registry. Each patient was randomly matched on age, sex, and calendar time to five general population comparators. Patients were observed for two years before and after TNFi initiation. All ICD-10 infection codes and information on filled prescriptions were extracted from nationwide registries. The data were split into four-year periods, and incidence rate (IR) per 1000 patient-years and IR ratios (IRR) of serious infections (SI) and prescriptions for each period were calculated.

Results

We identified 1387 individuals initiating their first TNFi treatment in 2003–2018 and 6936 general population comparators. The between-period IRR for SI was 0.48 (0.25–0.94, p=0.03) for the TNFi-treated patients in the last period compared to the first, while it was 1.05 (0.93–1.2) for antimicrobial prescriptions. The IRR for comparators was stable for SI but increased for antimicrobial prescriptions (1.2 (1.1–1.3)).

Conclusion

The study found that the IRR of serious infections associated with TNFi in patients with inflammatory arthritides has decreased over the years. The trend of diminishing SI incidence needs to be considered when analysing data over long periods or comparing recent research to previously published data.

Key words
rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, infections, tumour necrosis factor inhibitors

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Introduction

Inflammatory arthritides are a group of diseases that mainly cause joint inflammation, resulting in pain, swelling, and stiffness. The most common systemic inflammatory arthritides are rheumatoid arthritis (RA), psoriatic arthritis (PsA), and other spondyloarthritides (SpA). Patients with these conditions are at a higher risk of infection, which can be attributed to both the immune dysregulation attributed to the disease and the immunosuppressive treatments used to manage it (1-5). One such treatment is tumour necrosis factor inhibitors (TNFi), which have revolutionised the management of inflammatory arthritides over the past two decades. However, the use of TNFi therapy has been associated with an increased risk of infections, which can lead to severe complications and even mortality (6-13). These infections are usually classified into serious infections (SI) requiring hospitalisation, intravenous antibiotics, or resulting in death, and minor infections treated in an outpatient setting. In Iceland, infections are the third most common adverse effect of TNFi, accounting for 10% of treatment discontinuation in rheumatic patients (14). Therefore, monitoring and reporting on the infection risk associated with TNFi therapy and identifying trends over time is important.

The heightened risk of infections associated with TNFi in rheumatic patients is well documented (6-10, 13, 15-18). However, a potential trend of decreasing risk of SI in TNFi-treated rheumatic patients in recent years was reported in a large meta-analysis by Singh *et al*. (19). A similar observation was also noted in a single-centre study from Japan (20). Several factors could contribute to this trend, including greater clinical experience with TNFi, leading to improved patient selection for treatment. Moreover, the increased access to treatment due to the advent of biosimilars could facilitate the treatment of less severe disease. The earlier treatment with TNFi of less severe disease would lead to reduced exposure to glucocorticoids (GC) and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). While the first hypothesis is impossible to test objectively, the others lend themselves to analysing the available data.

We conducted a nationwide cohort study in Iceland to examine the temporal trends in overall infection rates in patients with inflammatory arthritides treated with TNFi therapy compared to the general population. We also investigated whether patients starting therapy more recently had less disease severity, reduced exposure to glucocorticoids and csDMARDs, and whether the number of patients beginning TNFi treatment had increased with the introduction of biosimilars.

Patients and methods

We performed a nationwide matched cohort study of adult biologic naïve patients with RA, PsA, and other SpA who received their first treatment episode with a TNFi from January 2003 through December 2018. 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. Data were collected for the study population two years before and after TNFi treatment for the patients or their matched reference date for the comparators, covering 2001 through 2020.

Data sources

Patients with inflammatory arthritides treated with bDMARDs in Iceland are registered in the nationwide Icelandic Registry of Biologic Treatment (ICEBIO). ICEBIO presently possesses information on over 98% of these patients, encompassing comprehensive patient characteristics, disease activity scores, and treatment details. Entries are done near treatment initiation, at six months, and then annually. The Icelandic Directorate of Health operates the Icelandic Hospital Discharge Register (IHDR) and the Icelandic Prescription Medicines Register (IPMR). Both are nationwide registers. The IHDR contains all hospital admissions from 1999 and outpatient visits from 2011. The IPMR covers nearly all filled prescriptions beginning in 2002, with decreased coverage before that year (21). From the IHDR, we extracted infor-

mation on all hospital admissions and outpatient visits with an International Classification of Diseases 10th revision (ICD 10) code for infection (Table I) occurring within two years before and after treatment initiation with TNFi. From the IPMR, we extracted prescription data for antimicrobials for all individuals in the study for two years before and two years after initiating the first TNFi treatment. Each prescription contained information about the date the prescription was filled at the pharmacy, the Anatomical Therapeutic Chemical Classification System (ATC) code, and the dose and administration form. All prescription medications with ATC codes starting with J01 (antibiotics), J02 (antimycotics), J05 (antivirals) and ATC codes P01AB01 (metronidazole, antibiotic), H02AB (glucocorticoids) and L04AX03 & L01BA0 (methotrexate) were included in the study. Prescriptions with ACT codes J04 (antimycobacterial), J05AR (anti-HIV) and J05AP (anti-hepatitis-C) were excluded. Antimicrobial and glucocorticoid use was further quantified by Defined Daily Doses (DDD) as specified by the World Health Organisation (WHO) at the time of data extraction in October 2021 (22). WHO defines DDD for medication as the average daily maintenance dose for its main indication in adults.

Exposure

Patients were considered exposed after the recorded date of the initiation of TNFi therapy. Patients and matched comparators were observed for two years before and after this index date or up to 30 days after treatment discontinuation, whichever came first.

Outcomes

The primary outcome was the occurrence of an SI, defined as a hospitalisation with an ICD-10 diagnosis for infection, a filled prescription for intravenous (IV) antibiotics, or treatment with intravenous antibiotics as an outpatient in the hospital. Multiple events occurring within 30 days were considered a single event. The number of prescriptions for antimicrobial agents was analysed as a secondary outcome.

Table I. ICD-10 codes used to identify infections.

A00-A99
B00-B99
G00-G07
H44.0, H44.1, H60.1, H60.2, H66.0, H70
I33.0
J00-J06, J09-J18, J09-018, J20.0-J22, J36, J39.0, J44.0, J85, J86
K35, K61.0- K61.4, K63.0, K63.1, K65.0- K65.3, K65.8, K65.9, K68.1, K75.0, K81, K83.0
L00, L02, L03, L05.0
M00, M01.0, M65.0, M65.1, M71.0, M71.1, M86
N10.0, N30.0, N34.0, N39, N70.0, N71.1, N72, N73, N75.1
O85, O86.0, 091
T80.2, T81.4, T82.6, T82.7, T83.5, T83.6, T84.5, T84.6, T84.7, T85.7

International classification of diseases 10th revision (ICD 10) codes for infections extracted from the Icelandic Hospital Discharge Register.

The primary and secondary outcomes were measured by counting the SI events and prescriptions per individual. These counts were used to calculate the incidence rate ratios between the periods before and after starting a TNFi, to compare the rates between patients and the matched comparison cohort, and to analyse further based on demographics, disease activity, and the year of treatment start.

Covariables and stratification

To construct multivariable models, variables such as age, sex, date of diagnosis, and date of TNFi treatment initiation were used, along with disease activity information from the start of TNFi therapy, including Health Assessment Questionnaire (HAQ) scores, Disease Activity Score 28-joint count and C-reactive protein (DAS28-CRP), methotrexate use, and the number of prescriptions for antibiotics and glucocorticoids. The patient groups were divided into four-year periods based on the year of TNFi initiation: 2003-2006, 2007-2010, 2011-2014, and 2015-2018.

Statistical analysis

The rate of SIs and antimicrobial use was compared by period. Infection rates (IR) between groups were compared by events per 1000 patient-years (py) calculated using the epiR package in R, and the exact Poisson test was used to test null hypotheses (23). Analysis of Variance (ANOVA) was used to examine differences in patient characteristics between periods. The distribution of quantitative variables was evaluated visually using histograms or Q-Q plots to determine normality. Predictors for infections were estimated using uni- and multivariable Poisson linear regression, with the number of infection events following TNFi as the dependent variable. Different models were built, treating the time of TNFi initiation as either a categorical (four-year period) or a linear variable (year). For the multivariable model, variables significant in the univariable analysis will be included along with age, time period, and biological gender. If multiple disease activity measures or HAQ scores were significant in the univariable analysis, the variable with the least missing data would be selected for the multivariable model. Comparable models were constructed for the comparators to compare possible trends in the general population. Missing data were handled with multiple imputations using chain reactions with the MICE package in R (24). All calculations are shown with a 95% confidence interval (CI) in brackets unless indicated otherwise. Continuous variables are reported as means, while categorical variables are presented as counts and percentages. A significance level of 0.05 was set. Given that our primary comparisons were predefined, no additional adjustments for multiple comparisons were applied.

All data were anonymised before analysis. Statistical analysis was performed in RStudio (version 2022.12.0+353; R Project for Statistical Computing, Vienna, Austria), and data preparation was carried out in Microsoft Excel (version 16.69.1; Microsoft Corporation, Washington, USA). The study protocol was accepted by the National Bioethi-

Table II. Patient and comparator characteristics between periods.

	2003-2006	2007-2010	2011-2014	2015-2018	Overall
Patients					
Number of individuals (n)	246	269	367	505	1387
Age in years, mean years (SD)	49.4 (12.8)	49.1 (14.0)	48.5 (14.3)	48.7 (15.0)	48.8 (14.2)
Sex Female (%)	62.2%	59.5%	56.4%	59.0%	59.0%
Years from diagnosis, mean (SD)	11.1 (10.2)	8.04 (9.11)	6.70 (8.39)	5.74 (8.06)	7.48 (8.98)
Diagnosis					
PsA	52 (21.1%)	70 (26.0%)	123 (33.5%)	175 (34.7%)	420 (30.3%)
RA	123 (50.0%)	124 (46.1%)	153 (41.7%)	183 (36.2%)	583 (42.0%)
SpA	71 (28.9%)	75 (27.9%)	91 (24.8%)	147 (29.1%)	384 (27.7%)
HAQ at baseline, mean (SD)	0.760 (0.609)	0.956 (0.698)	1.19 (0.649)	1.12 (0.610)	1.07 (0.650)
DAS28-CRP at baseline, mean (SD)	4.25 (1.50)	4.09 (1.32)	4.32 (1.18)	4.09 (1.23)	4.18 (1.27)
Doctor VAS score at baseline, mean (SD)	58.2 (17.0)	57.7 (15.5)	56.4 (18.9)	54.3 (21.2)	56.1 (19.0)
DDD of GC for 2 years following TNFi, mean (SD)	85.5 (155)	91.5 (161)	76.6 (158)	80.1 (147)	82.4 (154)
DDD of GC for 2 years before TNFi, mean (SD)	114 (164)	126 (195)	102 (178)	134 (208)	120 (191)
Comparators					
Number of individuals (n)	1227	1349	1833	2527	6936
Age, mean years (SD)	49.4 (12.8)	48.8 (14.3)	48.5 (14.2)	48.5 (15.1)	48.7 (14.3)
Sex, Female (%)	62.2%	59.7%	56.4%	58.9%	59.0%
DDD of GC for 2 years before the reference date, mean (SD)	0.0389 (0.532)	0.0770 (1.41)	0.106 (1.01)	0.250 (4.40)	0.141 (2.78)
DDD of GC for 2 years after the reference date, mean (SD)	0.0494 (0.694)	0.0528 (0.808)	0.112 (1.42)	0.127 (1.64)	0.0949 (1.31)

DAS28-CRP: Disease Activity Score 28-joint count and C-reactive protein; DDD: defined daily doses; GC: glucocorticoids; HAQ: Health Assessment Questionnaire; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SpA: spondyloarthritis; VAS: visual analogue score.

cal Committee and the Data Protection Authority in Iceland (Licence: VSN-18-008).

Results

Patients and comparators

We identified 1387 individuals who initiated their first treatment episode for inflammatory arthritis with a TNFi during the study period. Of these patients 59% were females, 583 (42%) were diagnosed with RA, 420 (30.3%) with PsA, and 384 (27.7%) with other SpA. The mean age was 48.8 (48.1–49.6), with 13% older than 65. Detailed demographics are shown in Table II, and differences between patient groups are shown in Supplementary Table S1. The mean follow-up time after TNFi initiation was 1.9 (1.88–1.91) years.

There were 6936 matched comparators for these patients. Their mean age was 48.7 (48.4–49.1), and 59% were females (Table II).

Infections

The patient group filled 7941 prescriptions for oral antimicrobials, 3585 before exposure to TNFi and 4356 after. The comparison cohort filled 4098 before the index date and 3852 after, for a total of 7950 prescriptions. The IR for filled antimicrobial prescriptions rose from 1292.4 (1250.4–1335.4) per 1000 py before TNFi treatment to 1657.1 (1608.2–1707), with an incidence rate ratio (IRR) of 1.28 (1.22–1.34, $p<0.001$). The IR for filled antimicrobial prescriptions for the comparators was 295.4 (286.4–304.6) per 1000 py before the reference date and 293 (283.8–302.4) after ($p=0.72$).

The patient group had 217 hospital admissions with an ICD-10 code for an infection, nine prescriptions for IV antimicrobials, and two treatment episodes in an outpatient clinic. After analysing the data, 139 SI (58 before *vs*. 81 after TNFi) were identified according to the study protocol. For the comparators, we identified 391 hospital admissions, three filled prescriptions for IV antibiotic, and 78 treatment episodes in outpatient clinics. Three hundred thirty-six serious infection events were identified (163 before *vs*. 173 after). The most frequent ICD-10 codes for SI for the TNFi-treated patients were lower respiratory tract infections (34, 25%), genitourinary infections (28, 21%), and skin and subcutaneous infections (20, 15%). For the comparators during the same reference period, the most frequent SI were genitourinary infections (47, 24%), lower respiratory tract infections (41, 21%) and abdominal cavity infections (28, 14%). The patients had 20.9 (15.9-27) SI per 1000 py before TNFi initiation, and the IR rose to 30.8 (24.5–38.3) per 1000 py after TNFi initiation, with an IRR of 1.47 (1.04–2.1, $p=0.027$). The comparators had an IR of 12.1 (10.3–14.1) SI per 1000 py before the reference date and 12.2 (10.4–14.3) after ($p=0.956$).

Analysis by period

The patient groups were divided into four-year periods based on the year of TNFi initiation: 2003-2006 (n=246), 2007-2010 (n=269), 2011-2014 (n=367), and 2015-2018 (n=505).

Analysis by variance (ANOVA) demonstrated that the patient groups were similar in terms of age, glucocorticoid use, DAS28-CRP, and physician visual analogue score (VAS) at baseline. The groups differed regarding HAQ scores at baseline and their time from diagnosis. The mean HAQ score at baseline rose from 0.76 (0.65–0.87) in the first period of 2003–2006 to 1.11 (1.06–1.18) in 2015-2018 ($p<0.001$). At the same time, the mean time from diagnosis to TNFi treatment changed from 11.1 (9.8–12.5) years to 5.7 (4.9–6.5) years ($p<0.001$) (Table II).

The IR per 1000 py for SI in the TNFi-treated group was 36 (21–57.7) in the first period and 22.4 (13.9–34.3) in the last (IRR 0.6, $p=0.17$) (Table III) while it decreased in the patients before TNFi

Table III. Incidence rates per 1000 patient years with 95% confidence intervals.

	2003-2006	2007-2010	2011-2014	2015-2018
Serious infections				
Patients after TNFi	36 (21–57.7)	40.6 (25.1–62.1)	31.3 (19.6–47.4)	22.4 (13.9–34.3)
Patients before TNFi	32.6 (18.4–50.6)	31.6 (18.4–50.6.5)	16.3 (8.4–28.6)*	12.8 (6.8–22)*
Comparators after reference date	9.8 (6.2–14.7)	15.8 (11.3–21.4)	10.5 (7.4–14.5)	12.8 (9.8–16.5)
Comparators before reference date	13.4 (9.3 -18.9)	13.4 (9.9-17.7)	9 (6.2-12.6)	10.5 (7.9-13.7)
Antimicrobrial prescriptions				
Patients after TNFi	1443 (1336-1555)	1547 (1442–1658)	1803 (1705–1905)**	1717 (1634–1803)**
Patients before TNFi†	981 (893–1074)†	1481 (1378–1590)	1420 (1334–1511)	1450 (1374-1529)
Comparators after reference date	268 (247–289)	266 (246–286)	288 (271-306)	325 (309-341)**
Comparators before reference date†	256 (236-276)†	277 (257-297)	290 (273-308)	329 (313–345)

†IR might be underestimated in the first period due to incomplete coverage of the Icelandic Prescription Medicines Register for the year 2001.
p-values are not calculated.
** $p<0.01$ when compared to the 2003-2007 group with an exact Poisson test. * $p<0.05$ when compared to the 2003-2007 group with an exact Poisson test.

initiation from 32.6 (18.4–50.6) in the first period to 12.8 (9.8–16.5) in the last (IRR 0.4, $p=0.016$). At the same time, the IR per 1000 py for the matched comparators remained stable both before the reference date, 13.4 (9.3–18:9) to 10.5 (7.9–13.7) (IRR 0.8, $p=0.3$), and after IR of 9.8 (6.2–14.7) to 12.8 (9.8–16.5) (IRR 1.3, $p=0.3$) (Table III). The IRR of SI in the TNFi-treated patients compared to comparators changed from 2.8 (1.5–5.3, $p<0.001$) in the first period to 1.7 (1.01–2.9, $p=0.04$) in the last period.

The IR for antimicrobial prescriptions increased in the patient group from 1442.5 (1346.3–1555) to 1716.6 (1633.7–1802.6) per 1000 py (IRR 1.2, $p<0.001$) and in the comparators from 278 (260.2–296.7) to 336.9 (318.7–355.8) NP per 1000 py (IRR 1.2, $p<0.001$) (Table III).

Multivariable analyses

In a univariate analysis, SI was positively associated with prior antimicrobial prescriptions, prior SI, baseline HAQ score, age, and glucocorticoid use. In contrast, the increasing length of TNFi treatment was associated with reduced IRR. Neither the DAS28-CRP score, methotrexate use, diagnosis, time from diagnosis, sex, physician VAS score, nor time period was significantly associated with SI. However, a non-significant trend towards decreased incidence rates in recent years was observed ($p=0.0523$) (Table IV). All significant associations from the univariable analysis, in addition to period, sex and diagnosis, were included in a multivariable model. In this model, the HAQ score, glucocorticoid use, age, prior infections, and period remained statistically significant predictors of SI after TNFi initiation. We observed a significant trend of decreasing IRR of SI with each passing year (IRR 0.95 (0.91–0.96), $p=0.03$), with patients initiating TNFi in the last four-year period having half the IRR of SI compared to patients in the first period (IRR 0.48 (0.25–0.94), $p=0.03$) (Table IV). For the matched comparators, previous infections, age, female sex, and glucocorticoid use were associated with a higher incidence of SI, while the period was not (Table V).

In the univariable analysis for antimicrobial prescriptions, prior antimicrobial prescriptions, baseline HAQ score, age, period and glucocorticoid use were associated with increased IRR. In contrast, male sex and SpA diagnosis were associated with reduced IRR. In the multivariable model adjusted for significant covariates on the univariable analysis, glucocorticoid use, prior antimicrobial prescriptions, and sex remained a statistically significant predictor of antimicrobial prescriptions after TNFi initiation. Patients initiating TNFi in the years 2011–2014 had an IRR of 1.1 (1.01–1.2, $p=0.036$) compared to patients in the first period, although no significant time trend was observed ($p=0.08$) (Table IV). For the matched comparators, previous infections, age, female sex, and glucocorticoid use were associated with a higher incidence of SI, with a trend of increasing number of prescriptions each year (IRR 1.02 (1.01–1.03), $p<0.001$) (Table V).

Discussion

In this nationwide registry study, we investigated time trends in the incidence of infections over 20 years, observing nearly 5,400 patient-years and 27,000 person-years in general population comparators. We found a significant declining trend in the incidence of SIs in recent years among patients with inflammatory arthritides who initiated treatment with TNFi. Patients initiating their treatment in 2015-2018 had an IRR of approximately half that of those starting their treatment in 2003–2006 (Fig. 1). Importantly, this trend was not wholly attributable to alterations in patient characteristics or disease activity during the periods studied, and the background rate of SIs for the general population comparators remained constant throughout the study duration.

This trend was not detected in multivariable models related to antimicrobial prescriptions despite an overall rise in the absolute incidence rate during the study period. Concurrently, the background incidence of antimicrobial prescriptions within the matched general population comparators increased.

The decreasing incidence of serious infections observed in our study may have several contributing factors. Throughout the course of the study, the interval between the diagnosis of rheumatic disease and the initiation of TNFi treatment decreased by nearly half. It is a reasonable assumption that patients with a shorter disease duration

Table IV. Regression models for the patients.

	Univariate IRR for serious infections	Multivariate IRR for serious infections. Time as catagorical variable	Multivariate IRR for serious infections. Time as linear variable	Univariate IRR for antimicrobrial prescriptions	Multivariate IRR for antimicrobrial prescriptions. Time as categorical variable	Multivariate IRR for antimicrobrial prescriptions. Time as linear variable
Age	1.037 (1.02-1.04)**	1.03 (1.01-1.04)**	1.03 (1.01-1.04)**	1.003 (1.0006-1.005)**	1 (0.998-1.003)	1 (0.998-1.003)
Sex						
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	0.7 (0.45-1.1)•	0.9 (0.5-1.5)	0.9 (0.52-1.5)	0.6 (0.56-0.64) **	0.7 (0.65– 0.75)**	0.7 (0.65– 0.75)**
Years from diagnosis	1.008 (0.98– 1.031)			0.997 (0.997-1.001)•		
HAQ at baseline	1.98 (1.36-2.88)**	1.73 (1.2-2.5)**	1.75 (1.22-2.5)**	1.2 (1.15-1.28)**	1.012 (0.97-1.06)	1.025 (0.97-1.09)
DAS28crp at baseline	1.19 (0.97-1.46)•			1.03 (0.995-1.05)•		
VAS doctor at baseline	1.01 (0.99-1.03)•			0.996 (0.994-0.998)**		
Time period						
2003-2006	1 (reference)	1 (reference)		1 (reference)	1 (reference)	
2007-2010	1.12 (0.6-2.17)	0.88 (0.45-1.73)		1.1 (0.97-1.2)	0.91 (0.82-1.01)•	
2011-2014	0.87 (0.46-1.66)	0.71 (0.37-1.29)		1.2 (1.1-1.4)**	1.1 (1.01-1.2)*	
2015-2018	0.6 (0.32-1.16)•	0.48 (0.25-0.94)*		1.4 (1.1-1.3)**	1.05 (0.96.-1.2)	
Year of TNFi initiation	0.96 (0.91-1)•		0.95 (0.91-0.96)*	1.012 (1.005-1.018)**		1.01 (0.999-1.013)•
Diagnosis						
PsA	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
RA	1.28 (0.778-2.173)	0.85 (0.48-1.52)	0.85 (0.48-1.53)	1.07 (0.99-1.15)•	1.02 (0.95-1.1)	1.02 (0.94-1.1)
SpA	0.81 (0.43-1.5)	1.35 (0.68-2.65)	1.36 (0.69-2.65)	0.87 (0.81-0.95)**	1.01 (0.92-1.1)	1.01 (0.92-1.1)
DDD for GC after TNFi	1.003 (1.002-1.003)**	1.002 (1.001-1.003)**	1.002 (1.001-1.003)**	1.001 (1.0004-1.0007)**	1 (1-1.001)**	1 (1-1.001)**
SIs before TNFi	2.42 (1.73-3.12)**	4.78 (1.81-13.3)**	4.78 (1.8 = 2-13.11)**	1 (0.87-1.1)		
NP of antimicrobials before TNFi	1.06 (1.006-1.101)*	1.06 (1.003-1.1)*	1.06 (1.004-1.1)*	1.1 (1.095-1.11)**	1.096 (1.091-1.1) **	1.095 (1.09-1.1) **
Methotrexate use (Yes)	0.7 (0.45-1.07)•			1.05 (0.99-1.12)•		
TNFi treatment length (months)	0.999 (0.998-1)*	0.96 (0.93-1.004)•	0.97 (0.93-1.006)•	1.05 (1.04-1.06)**	1.05 (1.04-1.06)**	1.002 (1.001-1.002)**

Incidence rate ratios (IRR) estimates with 95% CI through Poisson regression. Multivariate IRRs are adjusted significant parameters from univariate analysis, sex, diagnosis and time period.
• $p<0.25$, * $p<0.05$, ** $p<0.001$.
DDD: defined daily doses; GC: glucocorticoid steroids; HAQ: Health Assessment Questionnaire; NP: number of prescriptions; PsA: psoriatic arthirits; RA: rheumatoid arthritis; SI: serious infection; SpA: spondyloarthritis; TNFi: tumour necrosis factor inhibitors.

Table V. Regression models for the comparators.

	Univariate IRR for serious infections	Multivariate IRR for serious infections. Time as catagorical variable	Multivariate IRR for serious infections. Time as linear variable	Univariate IRR for antimicrobrial prescriptions	Multivariate IRR for antimicrobrial prescriptions. Time as catagorical variable	Multivariate IRR for antimicrobrial prescriptions. Time as linear variable
Age	1.05 (1.04-1.06)*	1.04 (1.03-1.05)**	1.04 (1.03-1.05)**	1.01 (1.004-1.009)	1.001 (0.99-1.003)	1.001 (0.999-1.003)
Sex						
Female	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Male	0.57 (0.4-0.79)**	0.62 (0.43-0.87)**	0.62 (0.44-0.86)**	0.85 (0.8-0.91)**	0.94 (0.88– 1.007)	0.93 (0.87– 1.003)*
Time period						
2003-2006	1 (reference)	1 (reference)		1 (reference)	1 (reference)	
2007-2010	1.62 (0.98-2.74)	1.81 (1.08-3.1)*		0.99 (0.89-1.1)	1.03 (0.92-1.46)	
2011-2014	1.08 (0.65-1.84)	1.26 (0.74-2.22)		1.1 (0.98-1.19)	0.91 (0.82-1.01)	
2015-2018	1.31 (0.82-2.16)	1.48 (0.9-2.51)		1.2 (1.1-1.3)**	1.2 (1.1-1.3)**	
Year of TNFi initiation	1 (0.97-1.003)		1.01 (0.97-1.04)	1.02 (1.01-1.03)**		1.02 (1.01-1.03)**
DDD for GC after TNFi	1.002 (1.001-1.003)**	1.002 (1.001-1. 003)*	1.002 (1-1.003)*	1.0028 (1.0026-1.0029)	1 (1-1.001)**	1.002 (1.002-1.003**)
SIs before reference date	2.25 (2.01-2.47)**	1.94 (1.68-2.2)**	1.9-1.66-2.15)**	1.6 (1.5-1.7)**	1.42 (1.3-1.54**)	1.44 (1.32-1.55)**
NP of antimicrobials before TNFi	1.11 (1.08-1.14)**	1.1 (1.05-1.13)**	1.09 (1.05-1.12)**	1.15 (1.147-1.154)**	1.15 (1.146-1.154) **	1.147 (1.143-1.15)**

Incidence rate ratios (IRR) estimates with 95% CI through Poisson regression. Multivariate IRRs are adjusted significant parameters from univariate analysis, sex, diagnosis and time period.
* $p<0.05$, ** $p<0.001$.
DDD: defined daily doses; GC: glucocorticoid steroids; NP: number of prescriptions; SI: serious infection.

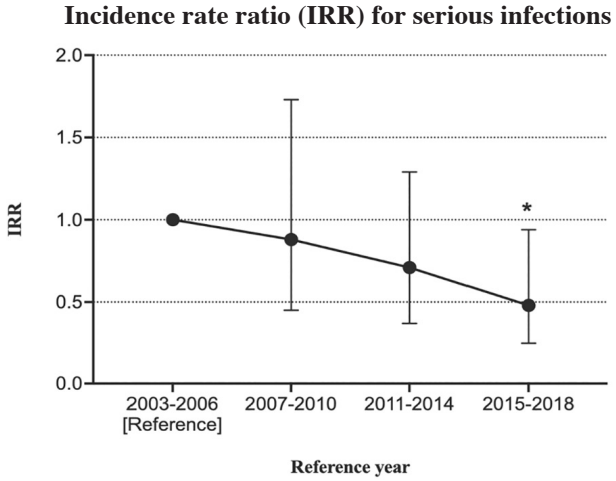

Fig. 1. Incidence rate ratio (IRR) estimates with 95% CI from Poisson regression for serious infections in TNFi treated patients by time period using 2003-2006 as reference. Individuals are observed up to two years following TNFi initiation (reference year). The model corrects for age, sex, previous infections, HAQ score, glucocorticoid use and diagnosis (RA, PsA or SpA).

would experience reduced exposure to glucocorticoids and a lower incidence of comorbidities associated with their condition. High disease activity, comorbidities, and glucocorticoid use are all associated with an increased risk of SI, and the risk attributed to glucocorticoids is particularly prominent when combined with TNFi (10, 11, 16, 25-28). The reduction in disease duration may explain why SI rates among the patients before TNFi treatment fell by over fifty percent between the initial and final assessment period, aligning with general population rates. This decline could lead to a lower risk of SI, as our models show that these pre-existing rates are significant risk factors during TNFi treatment (IRR 4.73 (1.8–13.3)).

A lower burden of comorbidities may partly explain the declining risk of SI over time. Since comorbidities are closely linked to antibiotic prescriptions, a corresponding decrease in antimicrobial use would be expected (29). Additionally, improved patient selection – favouring healthier individuals with fewer risk factors for TNFi treatment – should theoretically lead to fewer antimicrobial prescriptions. However, our models did not support this expectation. Instead, the absolute incidence rate of antimicrobial prescriptions among TNFi-treated patients increased over the study period, and the patients had more disabling disease. This suggests that while shifts in comorbidity profiles and patient selection may have contributed to the declining IRR of SI, they are unlikely to explain these findings fully.

An alternative explanation for the change in the incidence of infections is that healthcare providers have become more experienced with TNFi, coupled with increased patient education regarding their treatment. This might result in patients seeking medical help sooner and receiving antibiotics more promptly upon the onset of infections. Physicians might also have a higher threshold for admitting these patients due to infections than they did initially after the introduction of TNFi. Following the introduction of TNFi to clinical practice, an increased risk of tuberculosis infections was recognised (30-32). This inevitably raised concerns regarding increased infection risks in TNFi-treated patients. Studies in the early days of the TNFi era reported up to 50% lower 30-day mortality following hospitalisation in TNFi-treated RA patients than those on csDMARDs, possibly indicating a lower threshold for admitting these patients (10).

The patient groups have become increasingly balanced between RA (36%), PsA (35%), and SpA (29%) in the last period, in contrast to nearly half of all TNFi-treated patients having an RA diagnosis in the first period. Existing registry studies have demonstrated that TNFi-treated RA patients are at a heightened risk of SI compared to those with a PsA diagnosis (33). However, this study does not support that explanation, as our multivariable models did not demonstrate any significant difference in infection rates between patient groups, neither for SI nor for antimicrobial prescriptions.

The strengths of this study lie in its nationwide design and the completeness and reliability of the ICEBIO registry, along with the data provided by the Icelandic Directorate of Health. During the study timeframe, nearly all oral antibiotics, antivirals, and antifungals required a prescription, except a single fluconazole tablet for vaginal candidiasis and one treatment dose of valacyclovir for cold sores. This ensures comprehensive coverage of antimicrobial usage. Another strength resides in including SI treated with intravenous antibiotics as outpatients, as these infections have usually not been included in previous studies. Intravenous antibiotic treatment in an outpatient setting is becoming more common in clinical practice and may confound temporal trend analysis of SIs (34-36). However, our study might underestimate the SI incidence in the earliest years of the study period, as data on outpatient visits only go back to 2011.

This study has limitations that warrant consideration. It could not account for comorbidities or the potential influences of other csDMARDs aside from methotrexate. The study design prevents us from accessing ICD-10 codes from outpatient clinics and general practices, limiting our ability to link antimicrobial prescriptions to infections. Consequently, the data will contain antimicrobial prescriptions unrelated to ongoing infections. While less severe or viral infections, typically not treated with antimicrobials, are overlooked. Furthermore, the study does not consider the impact of changes in managing infections over time, such as the possible increased use of vaccines known to mitigate the risk of SI among rheumatic patients (37). Further, as the risk of serious infections is highest in the initial months after TNFi initiation, a possible survivor bias may arise, where patients at the highest risk discontinue treatment early, leaving only those with lower infection susceptibility to be observed (16). With our two-year follow-up, this could potentially dilute the reported absolute incidence numbers.

Iceland has a universal healthcare system where nearly all costs of medical treatment are covered by government

health insurance, ensuring equal access regardless of socioeconomic status. Additionally, Icelandic rheumatologists must apply to a central drug committee (CDC) to initiate and renew bDMARD treatment annually. The CDC grants licenses for specific bDMARDs based on a national tender process, typically favouring the most economical option. While rheumatologists can request alternative treatments, this system introduces a strong channelling bias toward TNFi as the first-line bDMARD treatment due to its historical cost-effectiveness. Variations in healthcare systems across countries could restrict straightforward comparisons, particularly where prescribing choices are less centralised or heavily impacted by private insurance. Nonetheless, our results are consistent with research from other nations that also indicate a declining risk of serious infections among TNFi users over time. This implies that the identified trend is not exclusive to Iceland and could signify broader advancements in patient selection, changing clinical practices, or biases within the healthcare sector.

In conclusion, this nationwide longitudinal study demonstrated that the incidence of serious infections associated with TNFi in patients with inflammatory arthritides has decreased in recent years. At the same time, antimicrobial use has remained stable. This trend of diminishing SI incidence rates must be considered when analysing data over long periods or comparing recent research to previously published data.

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