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Original article

Is the risk of infection higher during treatment with secukinumab than with TNF inhibitors? An observational study from the Nordic countries

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Abstract

Objectives. The positioning of secukinumab in the treatment of axial SpA (axSpA) and PsA is debated, partly due to a limited understanding of the comparative safety of the available treatments. We aimed to assess the risk of the key safety outcome infections during treatment with secukinumab and TNF inhibitors (TNFi).

Methods. Patients with SpA and PsA starting secukinumab or TNFi year 2015 through 2018 were identified in four Nordic rheumatology registers. The first hospitalized infection during the first year of treatment was identified through linkage to national registers. Incidence rates (IRs) with 95% CIs per 100 patient-years were calculated. Adjusted hazard ratios were estimated through Cox regression, with secukinumab as the reference. Several sensitivity analyses were performed to investigate confounding by indication.

Results. Among 7708 patients with SpA and 5760 patients with PsA, we identified 16 229 treatment courses of TNFi (53% bionaïve) and 1948 with secukinumab (11% bionaïve). For secukinumab, the first-year risk of hospitalized infection was 3.5% (IR 5.0; 3.9–6.3), compared with 1.7% (IR 2.3; 1.7–3.0) during 3201 courses with adalimumab, with the IRs for other TNFi lying in between these values. The adjusted HR for adalimumab, compared with secukinumab, was 0.58 (0.39–0.85). In sensitivity analyses, the difference from secukinumab was somewhat attenuated and in some analyses no longer statistically significant.

Conclusion. When used according to clinical practice in the Nordic countries, the observed first-year absolute risk of hospitalized infection was doubled for secukinumab compared with adalimumab. This excess risk seemed largely explained by confounding by indication.

Key words: spondylarthropathies, biologic therapies, immunosuppressants, DMARDs, epidemiology

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Rheumatology key messages

- In clinical practice, secukinumab was mainly used in biologic DMARD–experienced patients.
- In this setting, secukinumab was associated with higher absolute risk of hospitalized infections than adalimumab.
- The crude excess risk seemed largely explained by more frequent secukinumab use in difficult-to-treat patients.

Introduction

The IL 17-inhibitors (IL17i) secukinumab and ixekizumab are both approved for use in axial SpA (axSpA) and PsA. The EULAR recommendations for PsA currently place IL17 inhibitors (IL17i) alongside TNF-α inhibitors (TNFi) and ustekinumab as possible first-line biologic or targeted synthetic DMARDs (b/tsDMARDs) [1]. In contrast, the ACR guidelines for PsA and for axSpA, as well as the EULAR recommendations for axSpA, position TNFi before IL17i [2–4].

Since the effectiveness of IL17i and TNFi appears to be similar for the arthritis component of PsA and for the axial symptoms of axSpA [5–8], the choice of mode of action (MOA) may depend on other factors, such as disease features, comorbidities, safety concerns, or costs. Comparative studies of risk of infections during treatment with various types of biologic DMARDs (bDMARDs) have primarily been performed in RA, where they have revealed differences in the safety profiles that may have a direct impact on the choice of treatment for individual patients [9, 10]. For IL17i, safety data informing such choices are considerably sparser.

Considering the different MOAs of TNFi and IL17i, it could be expected that both the overall risk of serious infections and of specific types of infections (e.g. tuberculosis and candida) may differ between the drug classes [11–14]. However, randomized controlled trials (RCTs) comparing efficacy of IL17i and TNFi in PsA and psoriasis have reported similar overall rates of infections [7, 8, 15, 16]. Pooled analyses from a large number of RCTs on secukinumab suggest a rate of serious infections of 1.9 per 100 patient-years for PsA and 1.2 for AS [17], while similar analyses for adalimumab have indicated a rate of 2.8 for PsA and 1.4 for AS [18]. Although patients included in RCTs may not represent patients treated in routine care [19, 20], one large observational study comparing the occurrence of serious infections between PsA and psoriasis in patients treated with various DMARDs also reported similar rates for TNFi and IL17i [21].

The main objective of this study was to compare the overall risk of hospitalized infections during the first year of treatment with secukinumab and the various TNFi, in patients with SpA and PsA. As a secondary aim, we compared the risk of specific types of infections of particular interest (both hospitalized infections and infections in outpatient specialized care), namely pneumonia, urinary tract infections, tuberculosis, fungal infections, erysipelas, and herpes zoster.

Methods

Study design

This is an observational study based on prospectively collected register data.

Setting and data sources

Patients were identified in rheumatology registers in four of the Nordic countries: Denmark (DANBIO), Finland (ROB-FIN), Norway (NOR-DMARD) and Sweden (ARTIS/SRQ) [22]. From these registers, data on b/tsDMARD treatment courses and disease-specific measures were retrieved and linked to national registers to collect data on comorbidities and infections prior to treatment start and during treatment [23]. The linked data were available throughout years 2010–2018 for all countries apart from Denmark (data available until 31 July 2018). All ICD-codes used to identify patients, comorbidities and outcomes are presented in Supplementary Table S1, available at *Rheumatology* online.

Patients and treatments

All patients in the rheumatology registers with SpA or PsA (registered either as clinical diagnoses or as ICD-codes), starting secukinumab or a TNFi (adalimumab, certolizumab pegol, etanercept, golimumab or infliximab) in 2015 through 2018 were included. Each patient contributed with all different consecutive b/tsDMARD courses they started during this period, but switching between an originator and the corresponding biosimilar was disregarded, as were restarts following shorter interruptions of treatment (<60 days, e.g. due to surgery).

Clinical data at each treatment initiation were identified in the rheumatology registers as at the registered visit closest to the treatment start-date, within a window of –30 to +14 days. Previous comorbidities, registered within 5 years before treatment start, were identified in national registries for the following conditions: malignancy, diabetes, chronic pulmonary disease, congestive heart disease, myocardial infarction, kidney failure, and hip/knee prosthesis. From this a 'comorbidity score' (0, 1, 2+) was calculated for each patient by adding together the number of different comorbidities.

Follow-up

Patients were followed from the start-date of each treatment course (=baseline), until the first of the following: 12 months thereafter, 31 December 2018 (31 July 2018

for Denmark) or 90 days after treatment discontinuation. The follow-up was extended to 90 days after discontinuation in order to include infectious episodes occurring during treatment washout, but if another b/tsDMARD treatment was started during this period, the follow-up for the previous course was censored at the start of the subsequent treatment.

Outcomes

The main outcome was the first hospital discharge during follow-up listing an infection as a main or contributory discharge diagnosis (i.e. a hospitalized infection). The secondary outcome was the first infection registered during follow-up at hospital discharge or in specialized outpatient care (=hospitalized infections and infections in outpatient specialized care) of the following types: tuberculosis, pneumonia, herpes zoster, fungal infections, urinary tract infection, and erysipelas.

Statistics

Absolute risks of a first infection during treatment were described through cumulative incidence curves and percentages. We also calculated incidence rates (IR), and their 95% CIs, per 100 patient-years.

Hazard ratios (HRs) for a first infection were calculated through Cox regression in two models, comparing all TNFi with secukinumab as the reference. It was decided a priori to focus on adalimumab as the main comparator, since adalimumab is commonly used as an active comparator in clinical trials, and as a direct comparator in head-to-head studies. First, a basic model was used, adjusted only for sex and baseline age (continuous with a quadratic parameter). Second, a fully adjusted model was used, additionally adjusted for number of previous b/tsDMARDs (0, 1, 2, 3 and 4+) and the following baseline factors: disease duration (<1, 1–4, 4–10, >10 years), history of any registered infection (hospitalized infections and infections in outpatient specialized care) up to 5 years before treatment start (yes/no), the comorbidity score, concomitant use of conventional synthetic DMARDs (csDMARDs) (yes/no) and corticosteroids (yes/no), and disease characteristics: patient global visual analogue scale assessment of disease activity (VAS-global, 0–100 mm), HAQ, swollen joint count (0–28) and tender joint count (0–28) (all categorized according to quartiles and a fifth missing category). These disease characteristics were selected to capture disease severity with generic variables applicable in both SpA and PsA. The fully adjusted analysis also included country as strata. In the combined analyses of SpA and PsA, disease type (SpA or PsA) was included in the model as an additional covariate. Robust standard errors were used to adjust for multiple treatments per patient.

No IR or HR estimates were calculated for outcomes with fewer than 10 events in either of the exposure groups. Heterogeneity across the included countries was assessed though a random effects meta-analysis based on the main adjusted Cox model, with SpA and PsA combined and comparing adalimumab with secukinumab. The main objective was assessed for SpA and PsA combined as well as stratified.

Sensitivity analyses

In order to further explore the main outcome and to accommodate confounding by indication, four sensitivity analyses were performed based on the main outcome, also including a comparison between secukinumab and the combined TNFi cohort. First, only previously bio-naïve patients were included. Second, since patients starting secukinumab had (on average) more previous b/tsDMARD treatments, we performed an analysis restricted to patients who were starting their second or more bDMARD treatment. In this analysis, all patients with a previous infection (hospitalized infections and infections in outpatient specialized care, up to 5 years prior to treatment start) were also excluded. Third, the analyses were restricted to patients starting treatment in 2016 or later (secukinumab was first available 2015), on the assumption that patients starting a newly introduced drug may differ from patients initiating drugs that have been available longer. Fourth, a Cox model was used, with inverse probability treatment weights (IPTWs), in which all covariates were included except for the number of previous b/tsDMARDs and disease duration, which were separately adjusted for, due to imbalance in the weights for these two variables.

Post-hoc analysis

Due to the unexpectedly high absolute 1-year risk of hospitalized infections found for secukinumab compared with adalimumab, we performed a post hoc analysis to explore the possible extent of residual confounding. In this analysis, we used data only from Sweden, where we had access to information on additional potential confounders, namely length of formal education, smoking status, civil status, use of antidepressive drugs in the year prior to treatment start, as well as a longer follow-up (until 31 December 2020). Based on this data, we performed a series of Cox regression analyses comparing the hazard of hospitalized infections for secukinumab with adalimumab, gradually adjusting for additional confounders (for definitions see Supplementary Fig. S1, available at *Rheumatology* online).

Statistical programs

Statistical analyses were performed in SAS (version 9.4) and Stata (version 16.1).

Ethical approval

Appropriate ethical and/or data protection committees in each country approved of the study. Denmark: ethical approval is not required for registry studies (komitélovens §14, stk. 2, www.nvk.dk), Capital Region

Data-protection Office RH-2015-209, I-suite 04145; Finland: the Helsinki University Hospital coordinating Ethics Committee, 73/13/03/00/2014; Norway: Regional Ethics Committee of South Eastern Norway, 2011/1339 and 2017/243; Sweden: ethical review board Stockholm, 2015/1844-31/2). Informed written consent for the reporting of anonymized registry data for research purposes was not required according to the approval committees, apart from in Norway where such approval was required (and collected) for patients included after 2012.

Patient and public involvement

This study emanated from an international rheumatology registry collaboration (Nordic Register Pilot), in which patients were involved, but this specific study was designed without patient participation.

Results

A total of 13 468 patients were included, contributing 18 177 treatment courses (10 393 SpA and 7784 PsA). Patients starting secukinumab were on average older compared with patients starting TNFi, had higher baseline disease activity scores, were more frequently b/tsDMARD experienced, more often treated with corticosteroids and had a higher comorbidity burden (Table 1). Higher proportions of patients starting secukinumab had previous infections (either hospitalized infections or infections in outpatient specialized care) in the last 5 years, compared with patients starting treatment with TNFi (infliximab, in particular) (Table 1). For missingness of baseline data, see Supplementary Table S2, and for baseline characteristics of previously bio-naïve patients, see Supplementary Table S3, both available at *Rheumatology* online.

Hospitalized infections

For SpA and PsA combined, the crude cumulative incidence curves suggested a higher risk of hospitalized infections during the first year of treatment with secukinumab compared with adalimumab (Fig. 1). The absolute first-year risk of a hospitalized infection was 3.5% (69 events) for secukinumab, compared with 1.7% (54 events) for adalimumab, with the risks of the other TNFi falling in between these values. This corresponded to a crude IR for hospitalized infections during the first year of 5.0 (3.9–6.3) per 100 patient-years for secukinumab and 2.3 (1.7–3.0) for adalimumab, with the rates for the other TNFi falling in between these two rates (Table 2). IRs were generally higher for PsA compared with SpA, but had similar patterns across the bDMARDs.

Compared with secukinumab, the fully adjusted HR for hospitalized infections was 0.58 (0.39–0.85) for adalimumab and 0.63 (0.45–0.89) for etanercept. For the other TNFi, no statistically significant differences compared with secukinumab were observed in the fully adjusted analyses (Table 2). There were differences in the magnitude of the HR comparing adalimumab with secukinumab across the included Nordic countries, but the direction was consistent (except for Denmark), and no statistically significant heterogeneity was observed (Fig. 2).

Sensitivity analyses

The results of the sensitivity analyses (Fig. 3) confirmed those of the main analysis, with secukinumab being associated with a higher hazard of hospitalized infections, compared with adalimumab, although statistical significance was sometimes lost. The lowest HR for the TNFi, compared with secukinumab, were found in the previously bio-naïve patients, while the difference decreased in models further accounting for additional potential confounders, including number of previous b/tsDMARD courses. The results of the comparison with the combined TNFi cohorts were in line with those of adalimumab.

Types of infection

Analyses by type of infection (hospitalized infections and infections in outpatient specialized care) suggested similar, low, rates of pneumonia, urinary tract infection and fungal infection during treatment with secukinumab and the s.c. TNFi. For infliximab, a higher rate of pneumonia was observed compared with secukinumab, with an adjusted HR of 3.37 (1.69–6.72), as well as a lower rate of fungal infections, HR 0.42 (0.20–0.88) (Table 3). The numbers of events for herpes zoster, erysipelas and tuberculosis were too low to allow for meaningful comparisons; no registered occurrence of tuberculosis was found during treatment with secukinumab.

Post hoc analyses

The Cox regression analysis performed on Swedish data for 2015 through 2020 included 6095 patients, contributing 1869 treatment courses with secukinumab and 5040 courses with adalimumab. Overall, 71 (3.8%) events of a first hospitalized infection were registered for secukinumab, and 99 (2.0%) for adalimumab, resulting in an IR of 4.8 (95% CI 3.8, 6.1) for secukinumab and 2.4 (2.0, 3.0) for adalimumab. The crude HR, comparing adalimumab with secukinumab, was 0.49 (95% CI 0.36, 0. 68), but adding additional covariates gradually reduced the HR to 0.80 (0.57, 1.14) in the fully adjusted model, which was very similar to the results when applying the fully adjusted model from the main analyses to this dataset (HR 0.79; 0.55–1.12) (see Supplementary Fig. S1, available at *Rheumatology* online for details).

Discussion

In this study, including 13 468 patients with SpA and PsA from the Nordic countries, we observed a doubled absolute first-year risk of hospitalized infections among individuals initiating treatment with secukinumab compared with adalimumab, with the risk for the other four

Table 1 Baseline characteristics of patients starting secukinumab or a TNF-inhibitor in 2015 through 2018

	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
SpA						
N	806	1898	980	2994	1170	2545
Age, mean (S.D.), years	47 (13)	43 (13)	42 (13)	43 (14)	42 (13)	43 (13)
Sex, men *n* (%)	372 (46)	997 (53)	462 (47)	1503 (50)	660 (56)	1402 (55)
Country *n* (%)						
Denmark	147 (18)	256 (14)	283 (29)	552 (18)	216 (19)	1253 (49)
Finland	101 (13)	241 (13)	107 (11)	202 (7)	278 (24)	124 (5)
Norway	61 (8)	31 (2)	240 (25)	219 (7)	52 (4)	229 (9)
Sweden	497 (62)	1370 (72)	350 (36)	2021 (68)	624 (53)	939 (37)
Number of previous of b/tsDMARDs:						
None, *n* (%)	65 (8)	847 (45)	400 (41)	1674 (56)	501 (43)	1590 (63)
One, *n* (%)	158 (20)	628 (33)	255 (26)	843 (28)	298 (26)	509 (20)
Two, *n* (%)	218 (27)	258 (14)	155 (16)	274 (9)	194 (17)	249 (10)
Three, *n* (%)	165 (21)	97 (5)	95 (10)	127 (4)	95 (8)	112 (4)
Four +, *n* (%)	200 (25)	68 (4)	75 (8)	76 (3)	82 (7)	85 (3)
Disease duration, mean (S.D.)	9.1 (9.6)	7.1 (9.5)	7.5 (9.8)	6.2 (9.4)	7.5 (9.0)	6.3 (8.8)
ASDAS-CRP, mean (S.D.)	3.4 (1.1)	3.0 (1.1)	3.2 (1.0)	3.1 (1.0)	3.2 (1.1)	3.3 (1.1)
BASDAI, mean (S.D.)	6.0 (2.4)	5.0 (2.4)	5.3 (2.3)	5.4 (2.2)	5.1 (2.5)	5.5 (2.3)
Patient VAS-pain, mm, mean (S.D.)	64 (23)	55 (26)	58 (24)	59 (24)	57 (25)	58 (25)
Patient VAS-global, mm, mean (S.D.)	66 (25)	56 (26)	61 (25)	60 (24)	56 (27)	62 (26)
TJC-28, mean (S.D.)	3 (4)	2 (3)	2 (4)	2 (4)	2 (4)	2 (4)
SJC-28, mean (S.D.)	1 (2)	1 (2)	1 (2)	1 (2)	1 (2)	1 (1)
CRP, mg/l, mean (S.D.)	13 (26)	11 (20)	10 (16)	10 (16)	12 (20)	12 (22)
HAQ, mean (S.D.)	1.1 (0.6)	0.8 (0.6)	1.0 (0.6)	0.9 (0.6)	0.9 (0.6)	0.9 (0.6)
Concomitant csDMARD:						
MTX, *n* (%)	56 (10)	73 (6)	77 (10)	103 (5)	82 (11)	265 (14)
SSZ, *n* (%)	23 (4)	50 (4)	41 (5)	72 (3)	51 (7)	115 (6)
Any csDMARD, *n* (%)	75 (13)	118 (10)	122 (16)	175 (8)	129 (17)	357 (18)
Oral CSs, *n* (%)	79 (14)	107 (9)	57 (7)	169 (8)	66 (9)	129 (7)
History of infection[a]:						
Last 5 years, *n* (%)	245 (30)	462 (24)	225 (23)	720 (24)	281 (24)	515 (20)
Last 3 years, *n* (%)	167 (21)	333 (18)	156 (16)	511 (17)	202 (17)	374 (15)
Last 1 year, *n* (%)	68 (8)	146 (8)	77 (8)	240 (8)	90 (8)	161 (6)
Comorbidity score, *n* (%)[b]						
0	699 (87)	1773 (93)	897 (91)	2751 (92)	1084 (93)	2336 (92)
1	82 (10)	105 (6)	57 (6)	199 (7)	73 (6)	173 (7)
≥2	25 (3)	20 (1)	26 (3)	44 (1)	13 (1)	36 (1)
PsA						
N	1142	1303	674	2726	549	1390
Age, years, mean (S.D.)	52 (12)	50 (13)	49 (12)	50 (13)	49 (13)	49 (13)
Sex, men *n* (%)	455 (40)	612 (47)	268 (40)	1213 (45)	250 (46)	619 (45)
Country *n* (%)						
Denmark	250 (22)	195 (15)	186 (28)	376 (14)	87 (16)	606 (44)
Finland	96 (8)	124 (10)	57 (9)	89 (3)	84 (15)	51 (4)
Norway	56 (5)	9 (1)	142 (21)	111 (4)	20 (4)	125 (9)
Sweden	740 (65)	975 (75)	289 (43)	2150 (79)	358 (65)	608 (44)
Number of previous of b/tsDMARDs:						
None, *n* (%)	153 (13)	566 (43)	268 (40)	1707 (63)	200 (36)	855 (62)
One, *n* (%)	272 (24)	405 (31)	175 (26)	653 (24)	145 (26)	295 (21)
Two, *n* (%)	263 (23)	189 (15)	101 (15)	212 (8)	98 (18)	115 (8)
Three, *n* (%)	204 (18)	68 (5)	72 (11)	84 (3)	55 (10)	61 (4)
Four +, *n* (%)	250 (22)	75 (6)	58 (9)	70 (3)	51 (9)	64 (5)
Disease duration, mean (S.D.)	9.5 (8.8)	7.3 (9.0)	8.2 (8.8)	6.5 (7.8)	9.2 (8.6)	7.6 (8.2)
DAPSA28, mean (S.D.)	29.7 (17.3)	24.0 (15.1)	26.6 (17.2)	24.8 (14.3)	24.4 (13.6)	26.1 (15.8)
Patient VAS-pain, mm, mean (S.D.)	64 (24)	56 (25)	57 (26)	58 (24)	59 (25)	58 (25)
Patient VAS-global, mm, mean (S.D.)	65 (23)	57 (26)	60 (26)	59 (24)	59 (25)	62 (25)
SJC-28, mean (S.D.)	3 (4)	2 (3)	2 (3)	2 (3)	2 (3)	2 (3)
TJC-28, mean (S.D.)	6 (6)	5 (6)	5 (5)	5 (5)	5 (5)	5 (6)

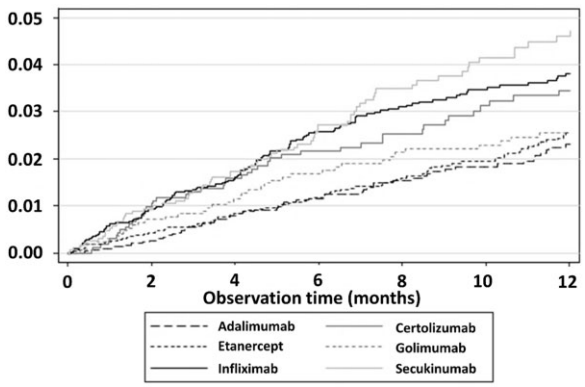
(continued)

Table 1 Continued

	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
CRP, mg/l, mean (S.D.)	11 (20)	9 (14)	12 (21)	10 (16)	11 (20)	11 (20)
HAQ, mean (S.D.)	1.2 (0.7)	1.0 (0.7)	1.1 (0.7)	1.0 (0.6)	1.0 (0.6)	1.1 (0.6)
Concomitant csDMARD						
MTX, *n* (%)	114 (15)	83 (10)	147 (29)	218 (11)	68 (17)	388 (36)
SSZ, *n* (%)	14 (2)	16 (2)	28 (6)	32 (2)	18 (5)	62 (6)
Any csDMARD, *n* (%)	144 (18)	114 (14)	191 (38)	271 (14)	84 (22)	463 (43)
Oral CSs, *n* (%)	148 (19)	114 (14)	72 (14)	251 (13)	50 (13)	124 (11)
History of infection[a]:						
Last 5 years, *n* (%)	389 (34)	330 (25)	170 (25)	691 (25)	149 (27)	317 (23)
Last 3 years, *n* (%)	280 (25)	244 (19)	128 (19)	519 (19)	99 (18)	244 (18)
Last 1 year, *n* (%)	123 (11)	110 (8)	66 (10)	236 (9)	44 (8)	96 (7)
Comorbidity score, *n* (%)[b]						
0	938 (82)	1150 (88)	582 (86)	2345 (86)	490 (89)	1195 (86)
1	154 (14)	131 (10)	73 (11)	315 (12)	48 (9)	155 (11)
≥2	50 (4)	22 (2)	19 (3)	66 (2)	11 (2)	40 (3)

[a]Any registered hospitalized infection or infection in outpatient specialized care. [b]Sum of number of different comorbidities registered within 5 years of: malignancy, diabetes, chronic pulmonary disease, congestive heart disease, myocardial infarction, kidney failure, and hip/knee prosthesis. ASDAS-CRP: Ankylosing Spondylitis Disease activity Score based on C-reactive peptide; b/tsDMARDs: biologic or targeted synthetic DMARDs; csDMARD: conventional synthetic DMARD; DAPSA28: 28-joint Disease Activity index for PsA; SJC-28: swollen joint count from 0 to 28; TJC-28: tender joint count from 0 to 28; VAS-global: patient global visual analogue scale assessment of disease activity; VAS-pain: visual analogue scale of pain.

Fig. 1 Crude cumulative incidence of hospitalized infections during the first year of treatment, SpA/PsA combined



TNFi falling in between. Sensitivity analyses attempting to further accommodate treatment channelling resulted in an attenuation of the HR and loss of statistical significance, suggesting that a differential use of the drugs might explain much of the observed excess risk for secukinumab. IRs for specific types of infections revealed no significant differences for secukinumab compared with the s.c. TNFi.

TNF is involved in a complex signalling system, exerting various effects on immune responses [11], in which treatment with TNFi is well known to increase the risk of serious bacterial (as well as milder) infections [24, 25], most commonly respiratory tract infections and especially during the first 6–12 months of therapy [26, 27], as well as causing reactivation of latent tuberculosis [12, 28]. On the other hand, IL17 is thought to be involved in upholding barrier function and mucosal protection [13], and conditions associated with IL17 malfunction may lead to chronic mucocutaneous candida infections [14]. Considering these differences, it is important to gain a better understanding not only of the relative risk of hospitalized infections, but also of specific types of infections, in order to better position secukinumab in the treatment strategy of SpA and PsA.

Several previous studies have assessed the risk of serious/hospitalized infections during treatment with TNFi in RA, with an IR ranging from 2.6 to 4.7 per 100 patient-years [10, 24, 27, 29–31] (see Supplementary Table S4, available at *Rheumatology* online). A recent comparison of risk for serious infections during TNFi treatment in RA and PsA, found an ~35% lower risk in PsA, which may at least partly be related to differences in sex and age distribution, as well as in concomitant treatment with conventional synthetic DMARDS (csDMARDs) and corticosteroids [29]. In studies focusing on PsA, IRs for serious infections of around 2.2 and 2.4 per 100 patient-years during TNFi treatment have been reported [21, 29]. These rates correspond well with the IRs for TNFi identified in the present study, and minor differences could be explained by different length of follow-up and distribution of type of TNFi.

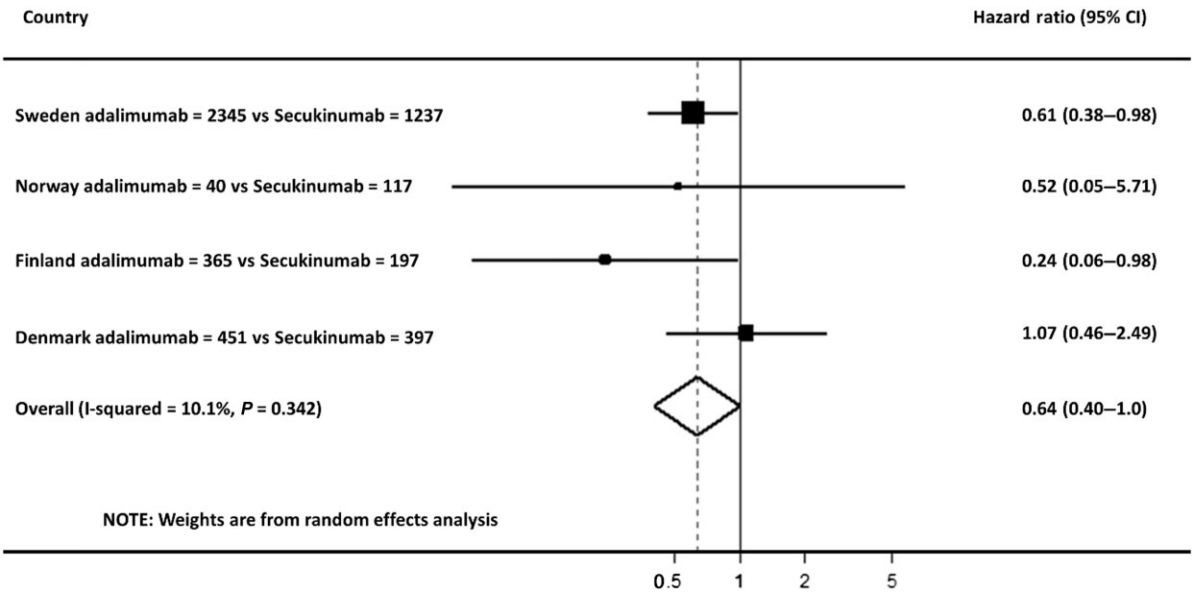
In two previous observational studies (Li *et al*. [21] and Jin *et al*. [32]) aiming to compare the risk of serious hospitalized infections during treatment with different b/tsDMARDs in patients with PsA and psoriasis, rates of infections on IL17i (combined) and secukinumab (specifically) were reported at 2.1 and 1.2 or 1.6 per 100 patient-years (two different data sources were

Table 2 Risk, incidence rates and hazard ratios of hospitalized infections

	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
SpA and PsA combined						
N	1948	3201	1654	5720	1719	3935
Events, *N* (%=absolute risk)[a]	69 (3.5%)	54 (1.7%)	46 (2.8%)	105 (1.8%)	38 (2.2%)	123 (3.1%)
Person-years	1380	2340	1230	4150	1390	2950
IR per 100 person-years (95% CI)	5.0 (3.9, 6.3)	2.3 (1.7, 3.0)	3.7 (2.7,5.0)	2.5 (2.1, 3.1)	2.7 (1.9, 3.8)	4.2 (3.5, 5.0)
HR, basic model (95% CI)[b]	Reference	0.46 (0.32, 0.66)	0.72 (0.48, 1.08)	0.51 (0.38, 0.70)	0.54 (0.35, 0.82)	0.84 (0.61, 1.15)
HR, fully adjusted (95% CI)[c]	Reference	0.58 (0.39, 0.85)	0.88 (0.57, 1.37)	0.63 (0.45, 0.89)	0.67 (0.43, 1.02)	1.02 (0.72, 1.44)
SpA						
N	806	1898	980	2994	1170	2545
Events, *N* (%=absolute risk)[a]	23 (2.9%)	31 (1.6%)	25 (2.6%)	53 (1.8%)	27 (2.3%)	82 (3.2%)
Person-years	560	1400	730	2170	960	1920
IR per 100 person-years (95% CI)	4.1 (2.6, 6.1)	2.2 (1.5, 3.1)	3.4 (2.2, 5.0)	2.4 (1.8, 3.2)	2.8 (1.9, 4.1)	4.3 (3.4, 5.3)
HR, basic model (95% CI)[b]	Reference	0.50 (0.29, 0.87)	0.74 (0.41, 1.33)	0.59 (0.36, 0.96)	0.62 (0.35, 1.09)	0.99 (0.62, 1.58)
HR, fully adjusted (95% CI)[c]	Reference	0.69 (0.40, 1.21)	0.90 (0.48, 1.69)	0.79 (0.47, 1.32)	0.84 (0.46, 1.51)	1.36 (0.82, 2.27)
PsA						
N	1142	1303	674	2726	549	1390
Events, *N* (%=absolute risk)[a]	46 (4.0%)	23 (1.8%)	21 (3.1%)	52 (1.9%)	11 (2.0%)	41 (3.0%)
Person-years	820	940	500	1980	430	1030
IR per 100 person-years (95% CI)	5.6 (4.1, 7.5)	2.5 (1.6, 3.7)	4.2 (2.6, 6.4)	2.6 (2.0, 3.4)	2.5 (1.3, 4.6)	4.0 (2.8, 5.4)
HR, basic model (95% CI)[b]	Reference	0.45 (0.27, 0.77)	0.77 (0.44, 1.35)	0.47 (0.31, 0.71)	0.46 (0.22, 0.96)	0.72 (0.46, 1.13)
HR, fully adjusted (95% CI)[c]	Reference	0.59 (0.34, 1.03)	1.07 (0.60, 1.92)	0.59 (0.37, 0.93)	0.57 (0.28, 1.20)	0.88 (0.54, 1.42)

Combined analyses and stratified analyses for SpA and PsA during the first year of treatment. [a]Number (%) of SpA and PsA patients with a hospitalized infection during follow-up. [b]Basic model adjusted for age and sex. [c]Fully adjusted model adjusted for sex, country and baseline: age, number of previous b/tsDMARDs, duration of the disease, history of infection in the last 5 years, comorbidity score (see Methods), concomitant csDMARD and CSs, global health score, HAQ, pain score, number of swollen and tender joint counts (0–28). In the combined analyses, disease type (SpA/PsA) was also adjusted for. b/tsDMARDs: biologic or targeted synthetic DMARDs; csDMARD: conventional synthetic DMARD; HR: hazard ratio; IR: incidence rate.

FIG. 2 Meta-analysis assessing heterogeneity of the hospitalized infections across the included countries



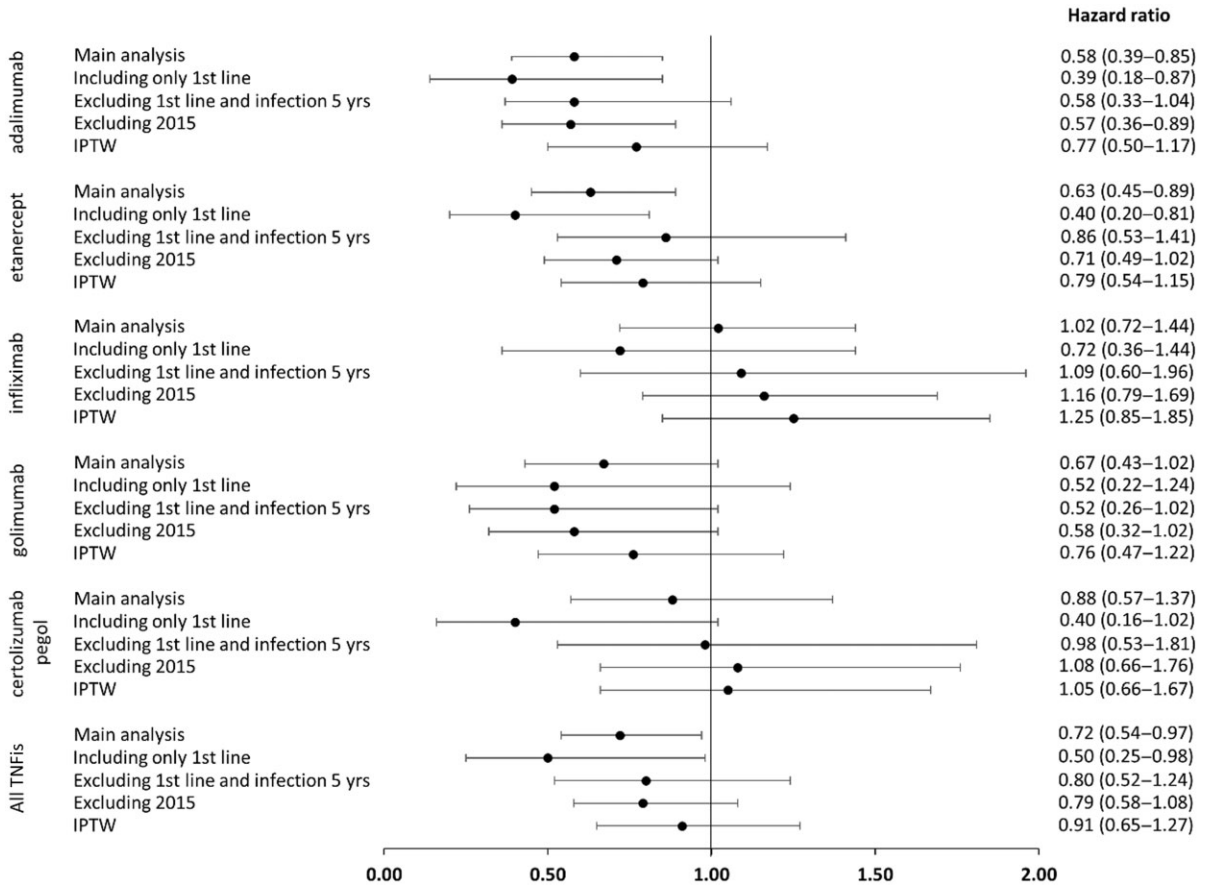
Adjusted hazard ratio for hospitalized infections, comparing adalimumab with secukinumab (reference), SpA and PsA combined.

used in the study by Jin et al.), respectively. Both studies were based on a large number of patients, with extensive data on potential confounders, identified in insurance claims databases in the USA. In the first, Li *et al*. compared hospitalized infections in patients with PsA and psoriasis, treated with TNFi, IL17i and ustekinumab. In that study, the authors found no significant difference in risk comparing IL17i and TNFi, but a lower risk for ustekinumab [21]. A possible explanation for the differences compared with our results may be that combining the different TNFi types could cancel out within-class differences in infection risk. In the second study, Jin *et al*. similarly compared risks of hospitalized infections in patients with PsA and psoriasis, including the same treatments and also apremilast. Using ustekinumab as the comparator, the authors reported a higher risk for TNFi, IL17i and apremilast, and although no direct comparison of TNFi *vs* IL17i was performed, the rates were similar [32]. To understand the diverging results between these two studies and our study, differences in crude infection rates across cohorts/studies are of interest. In the study by Li *et al.*, the IRs of infections for IL17i *vs* TNFi were 2.1 *vs* 2.4, and in the study by Jin *et al.* for secukinumab *vs* adalimumab they were 1.23–1.61 *vs* 1.19–1.51, while in our study the IRs of adalimumab *vs* secukinumab were 2.3 *vs* 5.0. The similar IR for adalimumab/TNFi in our study and the previous studies, but the considerably higher IR for secukinumab, could suggest that secukinumab and TNFi are used differently in the USA from how it is used in the Nordic countries, or that thresholds and approaches towards when to hospitalize an infection differ.

Given our unexpectedly high rates of infections for secukinumab [18], we performed an additional post hoc analysis including only Swedish data. In this analysis, we had immediate access to a longer follow-up, and more extensive information on socio-economics and other potential confounders. The selection of confounders was partly based on a recent study developing a prediction model for serious infections during treatment with bDMARDs [33]. Gradually adding more confounders reduced the excess risk to 20% (not statistically significant).

Some limitations should be acknowledged. First, all comparisons of treatment outcomes in observational studies suffer from risk of confounding by indication. As expected, the patients treated with secukinumab were more biologic-experienced and older, but also had higher DASs and a higher frequency of prior infections (perhaps due to previously being treated with TNFi). Despite our efforts to accommodate and adjust for confounding by indication, some residual confounding is likely to remain. Second, although including a large number of patients, some of the stratified analyses were not powered to detect rare outcomes. In particular, the analyses stratified by type of infection were limited by few events. Further, in the analyses stratified by type of infection only, patients registered with an infection at hospital discharge or at a visit in specialized outpatient care were detected, and thus many milder cases would not be recorded (e.g. fungal infections or upper respiratory infections treated in primary care [34, 35]). Unfortunately, antibiotic prescription data was not available for the current study. Furthermore, smoking status, which may affect risk of infections, was not available in the combined Nordic data, but did not affect the results in the post hoc Swedish analyses. This may imply that smoking is

Fig. 3 Sensitivity analyses and hazard ratios of first hospitalized infection, with secukinumab as reference



Including the first year of treatment for SpA and PsA combined, using the same fully adjusted model as in the main analyses (except for analysis 4 = IPTW). Results shown for each of the TNFi and for all TNFi combined. Sensitivity analyses: 1. Previously bio-naïve patients. 2. Restricted to patients starting a ≥2nd b/tsDMARD treatment course and excluding patients with previous infection within 5 years prior to treatments start. 3. Only including treatment starts from 2016 or later. 4. Cox model with an IPTW-adjusted analysis. b/tsDMARD, biologic/targeted synthetic DMARD; IPTW, inverse probability treatment weighted; TNFi, TNF inhibitors.

not acting as a confounder with regard to type of treatment.

In this large observational study, we conclude that in the Nordic countries there is a low frequency of hospitalized infections during treatment with secukinumab or TNFi in SpA and PsA. In clinical practice, secukinumab was mainly used in bDMARD-experienced patients, and the doubled absolute risk in patients treated with secukinumab, compared with adalimumab (with the other TNFi falling in between) seemed to be partly or entirely explained by confounding factors.

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Table 3 Incidence rates and hazard ratios for different types of infections

	Secukinumab	Adalimumab	Certolizumab pegol	Etanercept	Golimumab	Infliximab
Pneumonia						
N	1948	3201	1654	5720	1719	3935
Events, *N* (%=absolute risk)[a]	12 (0.6%)	12 (0.4%)	14 (0.9%)	32 (0.6%)	8 (0.5%)	54 (1.4%)
Person-years	1410	2350	1250	4180	1400	2990
IR per 100 person-years (95% CI)	0.9 (0.4, 1.5)	0.5 (0.3, 0.9)	1.1 (0.6, 1.9)	0.8 (0.5, 1.1)	–	1.8 (1.4, 2.4)
HR, basic model (95% CI)[b]	Reference	0.66 (0.29, 1.52)	1.46 (0.64, 3.33)	0.97 (0.50, 1.89)	–	2.32 (1.21, 4.46)
HR, fully adjusted[c]	Reference	1.03 (0.45, 2.39)	2.03 (0.88, 4.67)	1.56 (0.79, 3.08)	–	3.37 (1.69, 6.72)
Urinary tract infections						
N	1948	3201	1654	5720	1719	3935
Events, *N* (%=absolute risk)[a]	23 (1.2%)	22 (0.7%)	16 (1.0%)	42 (0.7%)	15 (0.9%)	36 (0.9%)
Person-years	1400	2350	1250	4180	1400	2990
IR per 100 person-years (95% CI)	1.6 (1.0, 2.5)	0.9 (0.6, 1.4)	1.3 (0.7, 2.1)	1.0 (0.7, 1.4)	1.1 (0.6, 1.8)	1.2 (0.8, 1.7)
HR, basic model (95% CI)[b]	Reference	0.70 (0.38, 1.28)	0.98 (0.49, 1.96)	0.71 (0.42, 1.19)	0.89 (0.45, 1.76)	0.92 (0.53, 1.60)
HR, fully adjusted[c]	Reference	0.80 (0.43, 1.50)	1.43 (0.70, 2.90)	0.84 (0.48, 1.47)	1.02 (0.51, 2.03)	1.38 (0.78, 2.42)
Fungal						
N	1948	3201	1654	5720	1719	3935
Events, *N* (%=absolute risk)[a]	21 (1.1%)	23 (0.7%)	10 (0.6%)	40 (0.7%)	8 (0.5%)	15 (0.4%)
Person-years	1400	2350	1250	4180	1400	3000
IR per 100 person-years (95% CI)	1.5 (0.9, 2.3)	1.0 (0.6, 1.5)	0.8 (0.4, 1.5)	1.0 (0.7, 1.3)	–	0.5 (0.3, 0.8)
HR, basic model (95% CI)[b]	Reference	0.66 (0.36, 1.20)	0.50 (0.23, 1.10)	0.64 (0.37, 1.10)	–	0.35 (0.17, 0.69)
HR, fully adjusted[c]	Reference	0.64 (0.34, 1.22)	0.62 (0.27, 1.44)	0.60 (0.33, 1.09)	–	0.42 (0.20, 0.88)
Erysipelas						
N	1948	3201	1654	5720	1719	3935
Events, *N* (%=absolute risk)[a]	11 (0.6%)	6 (0.2%)	7 (0.4%)	19 (0.3%)	6 (0.4%)	7 (0.2%)
Person/years	1410	2350	1250	4190	1400	3000
IR per 100 person-years (95% CI)	0.8 (0.4, 1.4)	–	–	0.5 (0.3, 0.7)	–	–
Zoster						
N	1948	3201	1654	5720	1719	3935
Events, *N* (%=absolute risk)[a]	4 (0.2%)	2 (0.1%)	0 (0.0%)	4 (0.1%)	1 (0.1%)	4 (0.1%)
Person-years	1410	2360	1250	4190	1410	3000
Tuberculosis						
N	1948	3201	1654	5720	1719	3935
Events, *N* (%=absolute risk)[a]	0 (0.0%)	1 (0.0%)	1 (0.1%)	1 (0.0%)	2 (0.1%)	3 (0.1%)
Person-years	1410	2360	1250	4190	1410	3000

Results are presented combined for PsA and SpA and including both hospitalized infections and infections in outpatient specialized care, during the first year of treatment. Since the numbers of infection events only include the prespecified types of infections and include outpatient care, they are not directly comparable with the number of events in the main analysis. [a]Number (%) of patients with an infection during follow-up. [b]Basic model adjusted for age and sex. [c]Fully adjusted model adjusted for age, sex, disease type (SpA/PsA), number of previous b/tsDMARDs, duration of the disease, history of infection in the last 5 years, comorbidity score (see Methods), concomitant csDMARD and CSs, global health score, HAQ, pain score, number of swollen and tender joint counts (0–28). Country was added as strata. b/tsDMARDs: biologic or targeted synthetic DMARDs; csDMARD: conventional synthetic DMARD; HR: hazard ratio; IR: incidence rate.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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