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Anterior uveitis in patients with spondyloarthritis treated with secukinumab or tumour necrosis factor inhibitors in routine care: does the choice of biological therapy matter?

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ABSTRACT

Background The effect of interleukin 17-inhibitors on anterior uveitis (AU) in spondyloarthritis (SpA) is poorly understood. This study aimed to compare the risk of AU during treatment with secukinumab versus tumour necrosis factor inhibitors (TNFi).

Methods Patients with SpA starting secukinumab or a TNFi 2015 through 2018 were identified in the Swedish Rheumatology Quality Register. Occurrence of AU was identified based on diagnosis codes in outpatient ophthalmology care in the National Patient Register. The main outcomes were crude rates of AU-diagnoses per 100 patient-years, and adjusted HRs for AU, during treatment, in patients without AU during the year before treatment start (in order to reduce confounding by indication). HRs were adjusted for age, sex, history of AU and patient global assessment of disease activity.

Results Based on 4851 treatment starts (456 secukinumab; 4395 any TNFi), the rate of AU-diagnoses per 100 patient-years was 6.8 (95% CI 5.2 to 8.7) for secukinumab. Among the TNFi, the rate varied from 2.9 (95% CI 2.1 to 3.7) for infliximab and 4.0 (95% CI 3.3 to 4.9) for adalimumab to 7.5 (95% CI 6.7 to 8.4) for etanercept. The adjusted HRs for first AU (adalimumab as reference) were: secukinumab 2.32 (95% CI 1.16 to 4.63), infliximab 0.99 (95% CI 0.49 to 1.96), etanercept 1.82 (95% CI 1.13 to 2.93), golimumab 1.59 (95% CI 0.90 to 2.80) and certolizumab 1.12 (95% CI 0.44 to 2.83). Sensitivity analyses confirmed the pattern of higher AU rates with secukinumab and etanercept versus monoclonal TNFi.

Conclusion As used in clinical practice in SpA, secukinumab appears to be associated with a higher risk of AU, compared with the monoclonal TNFi and a similar risk compared with etanercept.

Key messages

What is already known about this subject?

- Tumour necrosis factor (TNF)-inhibitors protect against anterior uveitis flares in spondyloarthritis, with a more prominent protective effect of monoclonal TNF-inhibitors compared with etanercept.
- By contrast, the effect of interleukin-17 inhibitors on anterior uveitis is poorly understood.

What does this study add?

- In this nationwide observational cohort of patients with spondyloarthritis, monoclonal TNF inhibitors were more effective, compared with secukinumab and etanercept, in protecting against anterior uveitis.

How might this impact on clinical practice or future developments?

- In patients with spondyloarthritis, monoclonal TNF-inhibitors may offer better protection against recurrent flares of anterior uveitis, compared with secukinumab and etanercept.

INTRODUCTION

Among patients with spondyloarthritis (SpA), extra-articular manifestations are frequent. A recent meta-analysis reported that 18% of patients with radiographic axial SpA (axSpA) and 14% of patients with non-radiographic axSpA (nr-axSpA) had a history of anterior uveitis (AU), and that 7% and 6%, respectively, had a history of inflammatory bowel disease (IBD), while the frequency of psoriasis was 9% in both groups.[1]

Randomised controlled trials (RCTs) of treatment of axSpA typically focus on axial disease activity,[2–4] where the effect appears to be similar across the different tumour necrosis factor inhibitors (TNFi).[5] For secukinumab and ixekizumab, indirect comparison of the results from their pivotal RCTs, together with a large observational study,[6] suggest that the effect of interleukin 17-inhibitors (IL-17i) on axial disease is in line with that of TNFi.[2 3 7]

Whereas the effects on axial disease may be similar, the effects on other SpA manifestations seem to vary substantially. In general, IL-17i are more effective than TNFi in psoriasis,[8] and while monoclonal TNFi are effective in IBD,[9 10] the soluble TNF-receptor etanercept[11] and IL-17i are not.[12 13] For IBD, the initial RCTs even suggested aggravated disease after treatment with IL-17i.[12 13] Further, although IL12/23 inhibition (ustekinumab) is effective in psoriasis,[14] psoriatic arthritis[15] and IBD,[16] it appears to lack effect on

the axial component of axSpA,[17] highlighting the fact that the experience from TNFi cannot be uniformly extrapolated to inhibition of the IL-23/IL-17 axis.

For AU, TNFi reduces the frequency of flares in axSpA,[18 19] and the presence of AU has been linked to a better TNFi treatment retention,[20] but the protective effects regarding AU seem to be less for etanercept than for monoclonal TNFi.[19 21–24] Further, TNFi are effective in a wide range of other forms of uveitis,[25] while subcutaneous secukinumab is ineffective in non-SpA uveitis.[26] Based on currently available data, the 2019 American College of Rheumatology recommendations for management of axSpA therefore stress the need for more evidence regarding the role of IL-17i in the treatment of axSpA patients with AU.[27]

The objective of this nationwide study was to compare the risk of AU in patients with SpA treated with secukinumab or TNFi, in routine clinical care.

METHODS

Study design

Retrospective observational study on patients with SpA treated with secukinumab or TNFi in Sweden, based on prospectively collected national register data.

Data sources

Data linked through personal identification numbers, from four national registers in Sweden, were used: (1) The Swedish Rheumatology Quality register (SRQ), which prospectively collects data from routine rheumatology care, with a national coverage for biological disease-modifying antirheumatic drugs (bDMARDs) in SpA of almost 90%.[28] (2) The National Outpatient Register, collecting data from visits in outpatient specialised care since 2001. The coverage of the outpatient register is virtually complete for public specialised care, while some private care providers have incomplete reporting. In 2015–2018, 33%–39% of outpatient visits in specialised ophthalmology care were in private care.[29] (3) The Prescribed Drug Register, collecting complete patient-level data on prescribed drugs since 2005, at the time they are collected from a pharmacy.[30] (4) The Population Register, recording demographic data. All codes used to identify patients, outcomes and treatments are presented in online supplemental table S1.

Patients and treatments (exposure)

All patients with a diagnosis of ankylosing spondylitis (AS) or undifferentiated SpA (uSpA) in the SRQ, starting secukinumab or a TNFi (adalimumab, certolizumab, etanercept, golimumab or infliximab) between 1 Jan 2015 (secukinumab was introduced in 2015) and 31 December 2018 were identified. Each patient could contribute several treatment cohorts. This group is henceforth denoted 'overall cohort'.

In order to reduce the effect of confounding by indication, caused by channelling of patients with prior AU towards monoclonal TNFi, patients with an AU-diagnosis during the year prior to treatment start were then excluded, forming the 'main cohort' of the study.

Among the patients, a history of IBD was defined by >1 prior registered diagnosis of IBD in a department of gastroenterology or internal medicine. Similarly, psoriasis was defined by >1 prior diagnosis of psoriasis in dermatology care, or by a prior prescription for a psoriasis medication (to account for patients treated in primary care).

Follow-up

Follow-up for each treatment started at the date of treatment initiation, and ended at the first of: discontinuation of the treatment, end of study 31 December 2018, death or emigration.

AU (outcome)

All analyses of the primary and secondary outcomes are based on the 'main cohort', excluding patients with a diagnosis of AU in the year prior to treatment start.

The primary outcome was the rate of AU-diagnoses in outpatient ophthalmology care (based on the total number of all registered AU-diagnoses for each patient), per 100 patient-years, during the respective treatment. Each individual thus contributed with all his or her registered AU-diagnoses during the follow-up.

In addition, we constructed two AU-flare definitions, as previously described[24] : Flare definition 1—all registered visits with an AU-diagnosis separated by a gap of at least 90 days without any AU-diagnosis; Flare definition 2—all registered visits with an AU-diagnosis occurring at least 60 days after a previous registration (irrespective of any visits in-between).

The secondary outcome was the risk of a first registered AU-diagnosis in outpatient ophthalmology care during follow-up, assessed as HRs for each treatment in comparison to adalimumab (reference).

Statistical analyses

The rates for AU in the 'main cohort' were calculated per 100 patient-years, with 95% CI, using Poisson regression accounting for multiple events per individual.

HRs for risk of having a first registered AU-diagnosis during the respective treatment (in the 'main cohort') were determined through Cox regression with adalimumab as reference, crude and adjusted for age, sex, history of AU (yes/no) and patient global assessment of disease activity (quartiles and a missing category) at treatment start, including a robust sandwich estimate for the SEs to account for cases contributing more than one line of treatment. The variables were included on the basis of their potential role as confounders, where patient global assessment was chosen as a marker of disease activity, instead of the Bath Ankylosing Spondylitis Disease Activity Index or the Ankylosing Spondylitis Disease Activity Score, due to a higher proportion of missing data for the latter (table 1). The univariable association between hypothesised confounders and risk of AU are presented in online supplemental table S2. The assumption of proportional hazards was assessed through visual inspection of survival curves and through insertion of an interaction term with time in the models.

All statistical analyses were performed in SAS (V.9.4), and values of $p<0.05$ were considered statistically significant.

Sensitivity analyses

In order to further accommodate for confounding by indication, two sensitivity analyses were performed. The first analysis included all SpA patients who started treatment with adalimumab in 2004–2018 and who later stopped this treatment and within 1 year of discontinuation started secukinumab or one of the other TNFi. In this patient population the relative risk of AU on the subsequent treatments vs that on adalimumab were calculated, based on rate ratios for the rate of AU (as described for the primary outcome). The rate ratios were calculated through Poisson regression accounting for each individual contributing two consecutive treatment lines.

In the second sensitivity analysis, patients treated with secukinumab, adalimumab, golimumab or certolizumab in 2015–2018

Table 1 Baseline characteristics of patients starting secukinumab or a TNFi

	Secukinumab	Adalimumab	Etanercept	Infliximab	Golimumab	Certolizumab	Total
Treatment starts, n	**456**	**1006**	**1800**	**783**	**500**	**306**	**4851**
Sex, men, n (%)	190 (42)	507 (50)	909 (51)	405 (52)	289 (58)	124 (41)	2424 (50)
Age, years, mean (SD)	48 (13)	44 (14)	43 (14)	43 (14)	43 (14)	44 (14)	44 (14)
Diagnosis, AS n (%)	188 (41)	413 (41)	704 (39)	366 (47)	258 (52)	120 (39)	2049 (42)
BASDAI, mean (SD)	6.4 (2.0)	5.5 (2.1)	5.5 (2.0)	5.8 (2.0)	5.3 (2.3)	5.9 (2.1)	5.6 (2.1)
Missing n (%)	248 (54)	622 (62)	1053 (59)	462 (59)	283 (57)	190 (62)	2858 (59)
ASDAS, mean (SD)	3.4 (1.0)	3.0 (1.0)	3.0 (0.9)	3.2 (1.0)	3.0 (1.0)	3.2 (1.0)	3.1 (1.0)
Missing n (%)	257 (56)	669 (67)	1156 (64)	486 (62)	301 (60)	197 (64)	3066 (63)
Patient global assessment, mean (SD)	67 (21)	57 (23)	58 (22)	59 (23)	56 (24)	61 (23)	59 (23)
Missing n (%)	194 (43)	500 (50)	881 (49)	391 (50)	230 (46)	142 (46)	2338 (48)
CRP, mean (SD)	11 (22)	10 (16)	10 (16)	15 (29)	11 (20)	10 (16)	11 (20)
Missing n (%)	185 (41)	462 (46)	799 (44)	329 (42)	208 (42)	120 (39)	2103 (43)
Line of bDMARD treatment							
Line 1, n (%)	35 (8)	470 (47)	1202 (67)	539 (69)	242 (48)	79 (26)	2567 (53)
Line 2, n (%)	106 (23)	347 (34)	415 (23)	100 (13)	112 (22)	96 (31)	1176 (24)
Line 3, n (%)	129 (28)	109 (11)	93 (5)	86 (11)	76 (15)	65 (21)	558 (12)
Line ≥4, n (%)	186 (41)	80 (8)	90 (5)	58 (7)	70 (14)	66 (22)	550 (11)
IBD, n (%)	16 (4)	109 (11)	45 (3)	69 (9)	28 (6)	21 (7)	288 (6)
Psoriasis, n (%)	62 (14)	70 (7)	112 (6)	44 (6)	34 (7)	34 (11)	356 (7)
Previous AU, n (%)*	63 (14)	179 (18)	204 (11)	96 (12)	88 (18)	50 (16)	680 (14)
Concomitant csDMARDs							
Methotrexate, n(%)	73 (16)	168 (17)	255 (14)	215 (27)	77 (15)	47 (15)	835 (17)
Sulfasalazine, n (%)	27 (6)	80 (8)	164 (9)	71 (9)	41 (8)	30 (10)	413 (9)
csDMARD total, n (%)	102 (22)	251 (25)	414 (23)	282 (36)	119 (24)	82 (27)	1250 (26)

The table presents the data for the 'main cohort', excluding cases with a diagnosis of AU in the year prior to treatment start. Data were complete unless otherwise presented.
*Any registration of AU in outpatient ophthalmology care since start of the outpatient register in 2001.
AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; AU, anterior uveitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biological disease modifying anti-rheumatic drug; CRP, C reactive protein; csDMARD, conventional synthetic DMARD; IBD, inflammatory bowel disease; TNFi, tumour necrosis factor inhibitors.

were matched, 1:1 through propensity scores, with patients treated with etanercept (constituting the largest cohort to draw comparators from). The propensity scores were based on age, sex, line of treatment and history of AU (categorised, see online supplemental table S2), using a greedy match within a calliper of 0.2 SD of the logit of the propensity score, and trimming at the 2.5th and 97.5th percentile. Measures of disease activity were not included in the propensity score due to the high proportion of missing data. HRs for a first AU-diagnosis during treatment were determined within each pair of drugs with etanercept as reference, crude and adjusted for patient global assessment of disease activity (quartiles and a missing category) at treatment start.

Patient and public involvement

Patients were not involved in the planning or execution of the study.

RESULTS

In total, 3616 patients (53% men) contributed 4851 treatment starts in the 'main cohort' in 2015–2018. There was a trend towards higher disease activity at treatment start for secukinumab compared with the TNFi, and a higher proportion of patients with psoriasis in the secukinumab group (14% vs 6%–11% for TNFi), see table 1. IBD was less frequent among those starting secukinumab (4%) and etanercept (3%) compared with the other TNFi (in particular adalimumab, 11%) and conventional synthetic DMARDs were more commonly used together with infliximab compared with the other treatments. The majority of patients initiating a TNFi started it as their first or second bDMARD, while for secukinumab 69% had used at least two previous TNFi (table 1).

Occurrence of AU

Among all patients (overall cohort), regardless of AU occurrence in the year prior to treatment start, 21% had a history of AU during the past 10 years (lower part of table 2). For secukinumab this was 18%, and for adalimumab and etanercept 32% and 14%, respectively, suggesting that the choice of treatment was influenced by previous AU history.

Excluding patients with an AU-diagnosis in the year prior to treatment start (main cohort) resulted in less pronounced differences across treatments in terms of history of AU-diagnoses during the past 10 years (secukinumab 11% vs adalimumab 15%) (top part of table 2).

New-onset AU during treatment (occurrence of an AU-diagnosis in patients with no previous registration of such diagnosis in the outpatient ophthalmology register since 2001), occurred in only 1% of patients (0.8% in previously bio-naïve) (table 2). There were numerical differences in new-onset AU among the drugs, with adalimumab being the lowest at 0.5%, and secukinumab (1.3%), certolizumab (1.6%) and etanercept (1.2%) the highest, but with frequencies too low to draw any solid conclusions (table 2).

Primary outcome: incidence rates of AU

The rates for AU per 100 patient years are presented in figure 1. Etanercept, secukinumab and golimumab displayed higher rates (with non-overlapping CIs) compared with infliximab and adalimumab, for the rate of AU based on the total number of

Table 2 Occurrence of AU before and during treatment

Treatment	AU-diagnosis prior to treatment start		Patients with ≥1 AU-diagnosis during treatment			Follow-up days, mean
	Within 10 years	Within 1 year	All	New onset*	New onset* biologics-naïve†	
Main cohort: excluding patients with an AU-diagnosis in year prior to treatment start						
Secukinumab n=456, n (%)	52 (11)	0	13 (2.9)	5 (1.3)	1 (3.3)	367
Adalimumab n=1006, n (%)	154 (15)	0	25 (2.5)	4 (0.5)	2 (0.5)	485
Infliximab n=783, n (%)	80 (10	0	13 (1.7)	4 (0.6)	2 (0.4)	473
Etanercept n=1800, n (%)	171 (10)	0	52 (2.9)	19 (1.2)	9 (0.8)	454
Golimumab n=500, n (%)	73 (15)	0	22 (4.4)	5 (1.2)	4 (1.9)	689
Certolizumab n=306, n (%)	44 (14)	0	6 (2.0)	4 (1.6)	0	425
Overall cohort: all patients starting secukinumab or a TNFi in 2015–2018						
Secukinumab n=493, n (%)	89 (18)	37 (8)	31 (6)	5 (1.3)	1 (3.3)	380
Adalimumab n=1249, n (%)	397 (32)	243 (19)	143 (11)	4 (0.5)	2 (0.5)	490
Infliximab n=883, n (%)	180 (20)	100 (11)	54 (6)	4 (0.6)	2 (0.4)	473
Etanercept n=1898, n (%)	269 (14)	98 (5)	104 (5)	19 (1.2)	9 (0.8)	459
Golimumab n=562, n (%)	135 (24)	62 (11)	56 (10)	5 (1.2)	4 (1.9)	694
Certolizumab n=335, n (%)	73 (22)	29 (9)	25 (7)	4 (1.6)	0	420

*New-onset AU=AU-diagnosis registered during treatment in patients with no AU-diagnosis prior to treatment start (the denominator is the number of patients starting the respective treatment having no prior registration of AU since start of outpatient register in 2001).
†Previously biologics-naïve patients.
AU, anterior uveitis; TNFi, tumour necrosis factor inhibitors.

registered AU-diagnoses, and with varying degree of statistical significance for the two flare definitions. Details on number of AU-diagnoses/flares and follow-up times are presented in online supplemental table S3.

Secondary outcome: HRs of AU

The adjusted HRs for a first AU during follow-up indicated significantly higher risks for secukinumab (HR: 2.32; 95% CI 1.16 to 4.63) and etanercept (HR: 1.82; 95% CI 1.13 to 2.93), compared with adalimumab (reference); results for the other TNFi are presented in table 3. No evidence of non-proportionality was found.

Sensitivity analysis

In total, 1119 patients were included in the analysis comparing rate ratios of AU between a subsequent bDMARD treatment and a previous treatment with adalimumab. Of these, 74 patients were subsequently treated with secukinumab, 200 with infliximab, 516 with etanercept, 217 with golimumab and 112 with certolizumab (see online supplemental table S4). The rate ratios

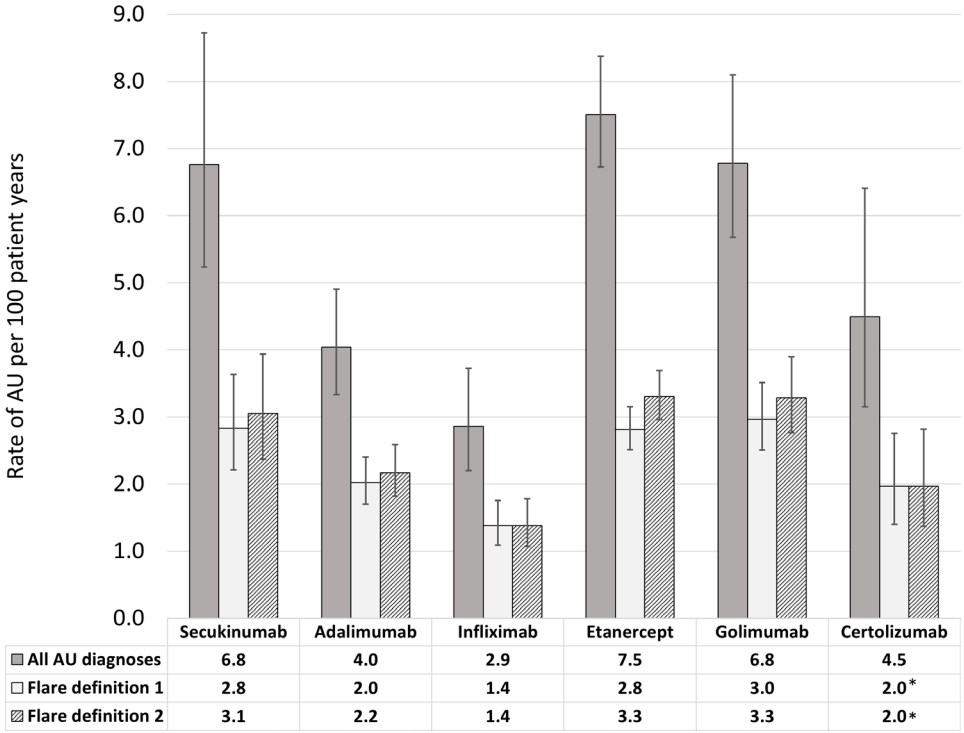

Figure 1 Rate of anterior uveitis (AU) per 100 patient-years during treatment. Error bars indicate 95% CI. *Rate based on <10 events, see online supplemental table S3. Flare definition 1: all registered visits with an AU-diagnosis separated by a gap of at least 90 days without any AU -diagnosis; flare definition 2: all registered visits with an AU-diagnosis occurring at least 60 days after a previous registration (irrespective of any visits in-between).

Table 3 HR of first on-treatment AU

	N with AU event/N total	Crude HR	Adjusted HR*
Adalimumab	25/1006	Ref	Ref
Secukinumab	13/456	1.53 (0.78–3.02)	2.32 (1.16–4.63)
Etanercept	52/1800	1.25 (0.77–2.01)	1.82 (1.13–2.93)
Infliximab	13/783	0.68 (0.35–1.32)	0.99 (0.49–1.96)
Golimumab	22/500	1.25 (0.71–2.21)	1.59 (0.90–2.80)
Certolizumab	6/306	0.90 (0.37–2.19)	1.12 (0.44–2.83)

*Adjusted for sex, age, previous history of AU and patient global assessment.
AU, anterior uveitis.

are shown in figure 2. Irrespective of AU definition, the rates were significantly higher after (vs before) switching from adalimumab to secukinumab, etanercept or certolizumab, but not after switching to infliximab or golimumab.

The propensity score matched pairs are presented in table 4. The pairs were well matched with regard to history of AU and line of treatment, but with some within-pair differences observed for disease activity (see online supplemental table S5 for standardised differences in the matched pairs). The crude and adjusted HR indicated a lower risk for AU on adalimumab, infliximab, golimumab and certolizumab (not statistically significant) compared with etanercept, but a similar risk for secukinumab.

DISCUSSION

In this nationwide observational study of SpA in clinical practice, treatment with adalimumab and infliximab were associated with a lower risk for AU compared with secukinumab and etanercept, but new-onset AU (in patient without previous AU) was very rare regardless of treatment. For certolizumab and golimumab the direction of the results was not consistent, and the higher crude

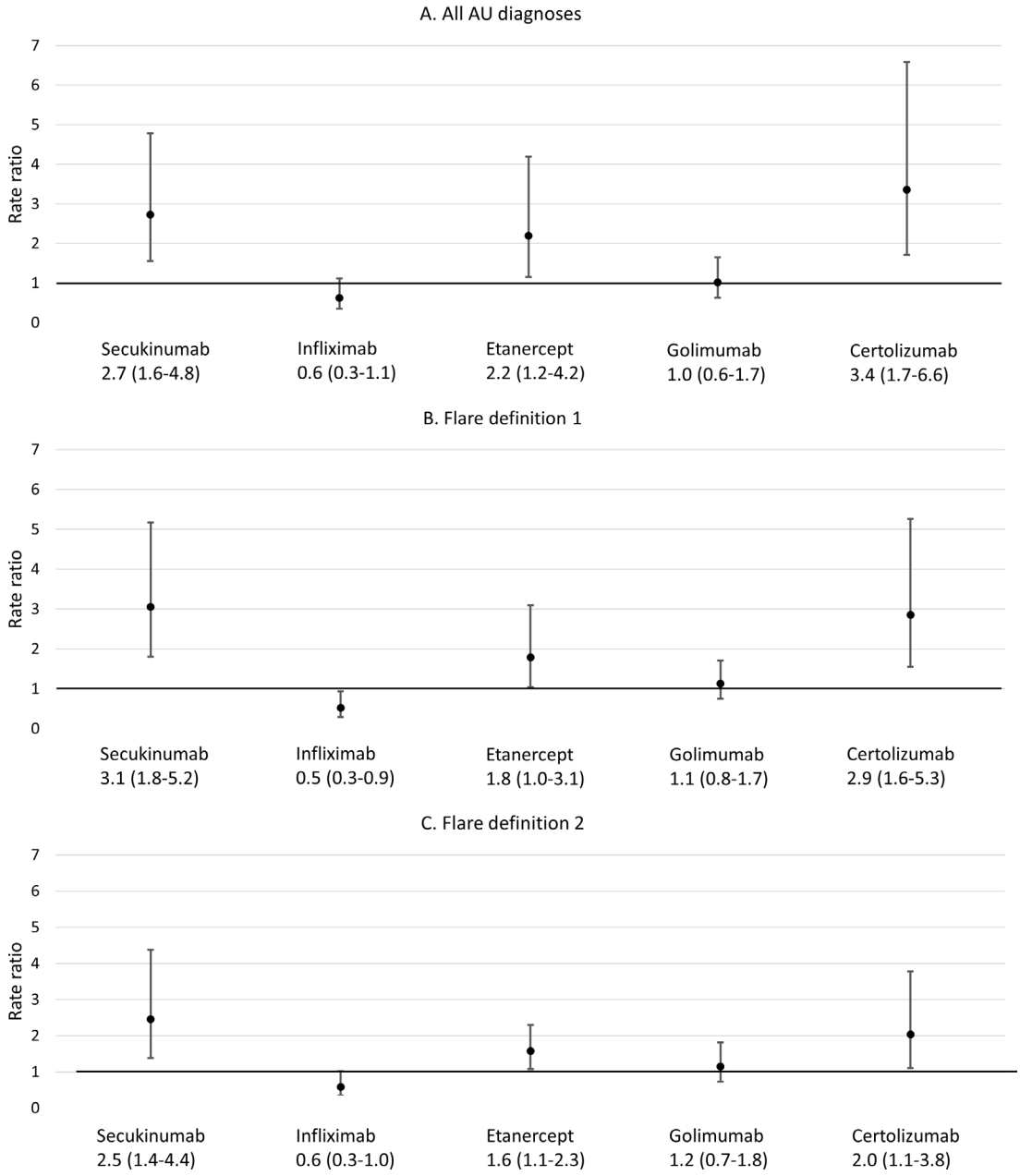

Figure 2 Rate ratios for anterior uveitis (AU), comparing each treatment with a prior adalimumab treatment. Flare definition 1: all registered visits with an AU-diagnosis separated by a gap of at least 90 days without any AU-diagnosis; flare definition 2: all registered visits with an AU-diagnosis occurring at least 60 days after a previous registration (irrespective of any visits in-between).

Table 4 Demographics and HR in propensity score matched analysis

	SEC versus ETN		ADA versus ETN		IFX versus ETN		GOL versus ETN		CER versus ETN	
N	251:251		826:826		745:745		473:473		240:240	
Line, mean (SD)	2.7 (1.0)	2.7 (1.0)	1.6 (1.0)	1.6 (1.0)	1.5 (1.1)	1.5 (1.0)	1.7 (1.0)	1.6 (0.9)	2.0 (1.0)	2.0 (1.0)
Age, mean (SD)	47 (13)	46 (13)	44 (13)	45 (13)	43 (14)	43 (14)	42 (14)	42 (13)	43 (14)	42 (12)
Sex, n (%) men	111 (44)	104 (41)	446 (54)	447 (54)	401 (54)	393 (53)	274 (58)	283 (60)	109 (45)	110 (46)
AU ever*, n (%)	47 (19)	52 (21)	217 (26)	211 (26)	138 (19)	150 (20)	119 (25)	128 (27)	54 (23)	58 (24)
AU 1 year 2, n (%)	19 (8)	20 (8)	79 (10)	74 (9)	59 (8)	58 (8)	48 (12)	55 (10)	24 (10)	24 (10)
Patient global assessment, mean (SD)	65 (22)	59 (24)	55 (24)	58 (23)	58 (24)	59 (23)	54 (25)	57 (21)	59 (24)	58 (23)
BASDAI, mean (SD)	6.2 (2.1)	5.5 (2.1)	5.3 (2.2)	5.5 (2.1)	5.6 (2.0)	5.5 (2.0)	5.1 (2.3)	5.4 (1.9)	5.8 (2.2)	5.7 (2.1)
AU events‡	18	20	55	79	35	60	42	42	19	19
HR AU-diagnosis	1.56 (0.80–3.05)	Ref	0.56 (0.40–0.78)	Ref	0.50 (0.34–0.73)	Ref	0.55 (0.36–0.85)	Ref	0.80 (0.39–1.67)	Ref
HR AU-diagnosis Adjusted§	1.59 (0.79–3.18)	Ref	0.55 (0.39–0.78)	Ref	0.50 (0.34–0.73)	Ref	0.53 (0.34–0.81)	Ref	0.79 (0.38–1.64)	Ref

The propensity scores were based on, age, sex, line of treatment and prior AU history, see the Methods section.
*Any registration of AU prior to treatment start.
†Any registration of AU in year prior to treatment start.
‡Number of patients with an event (=first AU-diagnosis) during follow-up.
§Adjusted for patient global assessment.
ADA, adalimumab; AU, anterior uveitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CER, certolizumab; ETN, etanercept; GOL, golimumab; IFX, infliximab; SEC, secukinumab.

rates could be biased. However, in the sensitivity analyses, golimumab performed in a similar way as the other two monoclonal TNFi in both analyses, while certolizumab was associated with a lower risk of AU compared with etanercept in one analysis. The other available IL-17i, ixekizumab, was not assessed in this study.

A better understanding of the performance of IL-17i in AU is important for the positioning of the treatment in SpA treatment recommendations. An early proof-of-concept study suggested a beneficial effect of intravenous secukinumab in non-infectious uveitis.[31] However, out of three subsequent RCTs investigating standard subcutaneous secukinumab in non-infectious uveitis, one failed to show a difference in efficacy compared with placebo, another was terminated due to lack of efficacy in interim analyses, and the last one terminated due to the results in the former two.[26] To determine if higher intravenous doses were more effective than subcutaneous doses, another small (N=37) trial compared 300 mg secukinumab subcutaneously every 2 weeks, with 10 mg/kg intravenously every 2 weeks, and 30 mg/kg intravenously every 4 weeks.[32] In that study, response rates were better for the intravenous high dose regimens. In the RCTs of AS, for both secukinumab[3] and ixekizumab[33 34] there were numerically more patients experiencing AU in the active treatment groups, although the frequencies were low. In the nr-axSpA RCTs the rates were similar in active treatment and placebo groups.[35 36] In a post hoc analysis of pooled data from the AS RCTs for secukinumab, including up to 4 years of treatment with secukinumab, 1.5% of the patients experienced a new-onset AU.[37] This is well in accordance with the 1.3% of secukinumab-treated patients in our study with a new-onset AU, also here with up to 4 years of follow-up.

When comparing AU incidence across studies, it is crucial to consider the proportion of patients with a history of AU, since previous AU is a strong risk factor for new AU flares (online supplemental table S2). For example, in one study the incidence of AU flares on adalimumab was 14 per 100 patient-years, with 43% having a prior history of AU,[38] while another study reports an on-adalimumab rate of 7.4, with 22% having a history of AU.[18] AU rates during treatment with golimumab was assessed in the GO-EASY study, where the flare rate was 2.2 per 100 patient-years, in AS patients of which 27% had a history of AU.[39] In our study, actively excluding patient with AU in the last year, 18% of the golimumab-treated patients had a history of AU, while we found flare rates at 3 per 100 patient-years. This might indicate that our flare definitions are more comprehensive and add additional precision, although overestimation is also a possibility. Whatever the reason, the higher flare rate seen here would not be expected to bias our comparisons across the different DMARDs. The effect of certolizumab on AU in axSpA has been published as interim results from the C-VIEW trial.[40] In that study, patients with at least one flare in the last year (ie, highly prone to develop new flares), were treated with certolizumab. The results indicated a significant reduction in AU-flares, with an on-treatment rate of 19 per 100 patient-years. The heterogeneity introduced by different study populations having different pretreatment risk of AU, makes indirect comparison across studies very difficult, and stresses the need for direct comparisons, as performed in our study.

Several limitations should be acknowledged. First, despite our efforts to reduce the impact of confounding by indication, residual confounding is likely to occur. Second, although we included a large number of patients, some of the subset analyses were presumably underpowered and especially for certolizumab the AU rates should be interpreted with caution due to few events. Third, AU-diagnoses in the register might not

be a sufficient measure of AU-flares. However, the number of registered AU-diagnoses overall should constitute an unbiased measure of AU burden/severity, and the two AU-flare definitions used may alleviate this limitation. Fourth, since the registrations in the SRQ are based on the International Classification of Diseases (ICD)-10 codes, nr-axSpA cannot be adequately discerned. Therefore AS and uSpA (including both nr-axSpA and peripheral SpA) were included instead, bearing in mind the different prevalence of AU.[41 42]

Fifth, since a comparable SpA population not treated with bDMARDs could not readily be identified in either of the data sources included in the study, a comparison with untreated patients was not possible. This precludes the possibility to discern if secukinumab is neutral (vs bDMARD-naïve SpA) in terms of risk for AU, is associated with an increased risk of AU, or if it has a protective effect of a relatively lower magnitude compared with the monoclonal TNFi. However, the very low rates of new onset AU on either of the bDMARDs would suggest the latter to be true.

Sixth, AU among patients seeking private ophthalmology healthcare (among which the reporting to the Patient Register may be lower than for public care providers) may not have been captured in this study. It is unlikely that this would bias our results, due to the general availability of subsidised healthcare in Sweden, although it cannot be ruled out that utilisation of private healthcare and level of health literacy may correlate with treatment choice and intensity for both SpA and AU.

Finally, misclassification is always present in register-based studies, but there is no reason to suspect that this would have introduced a bias with regard to bDMARD type.

This study also has strengths. To our knowledge, it is the first report comparing the occurrence of AU in a SpA population across the five TNFi and an IL17i, when used according to clinical routine. Furthermore, we have used several different approaches to minimise confounding by indication.

To conclude, regardless of type of TNFi or secukinumab, new-onset AU is rare during biological treatment. Furthermore, the monoclonal TNFi appear to be more effective choices for preventing AU in SpA patients, compared with etanercept and secukinumab.

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