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ORIGINAL RESEARCH

Exposure to specific tumour necrosis factor inhibitors and risk of demyelinating and inflammatory neuropathy in cohorts of patients with inflammatory arthritis: a collaborative observational study across five Nordic rheumatology registers

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ABSTRACT

Objective To compare incidences of neuroinflammatory events, including demyelinating disease (DML), inflammatory polyneuropathies (IPN) and multiple sclerosis (MS), in patients with rheumatoid arthritis (RA) or spondyloarthritis (SpA; including psoriatic arthritis) starting a tumour necrosis factor inhibitor (TNFi), investigating whether monoclonal TNFi antibodies (other TNFis (oTNFis)) confer higher risk than etanercept.

Methods This is an observational cohort study including patients from the five Nordic countries starting a TNFi in 2001–2020. Time to first neuroinflammatory event was identified through register linkages. We calculated crude incidence rates (cIR) per 1000 person-years and used multivariable-adjusted Cox regression to compare incidences of neuroinflammatory events overall and for DML, IPN and MS with oTNFi versus etanercept. We further examined individual TNFis and indications.

Results 33 883 patients with RA and 28 772 patients with SpA were included, initiating 52 704 and 46 572 treatment courses, respectively. In RA, we observed 135 neuroinflammatory events (65% DML) with cIR of 0.38 with oTNFi and 0.34 with etanercept. The HR of oTNFi versus etanercept was 1.07 (95% CI 0.74 to 1.54) for any neuroinflammatory event, 0.79 (95% CI 0.51 to 1.22) for DML, 2.20 (95% CI 1.05 to 4.63) for IPN and 0.73 (95% CI 0.34 to 1.56) for MS. In SpA, we observed 179 events (78% DML) with cIR of 0.68 with oTNFi and 0.65 with etanercept. The HR for any neuroinflammatory event, DML, IPN and MS was 1.06 (95% CI 0.75 to 1.50), 1.01 (95% CI 0.68 to 1.50), 1.28 (95% CI 0.61 to 2.69) and 0.94 (95% CI0.53 to 1.69), respectively.

Conclusion The cIRs of neuroinflammatory events are higher in SpA than in RA, but the choice of specific TNFi does not seem to play an important role in the risk of neuroinflammatory events.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Neuroinflammatory events, such as multiple sclerosis, have been reported in patients with rheumatoid arthritis, but particularly with psoriatic arthritis or spondyloarthropathies and during treatment with tumour necrosis factor inhibitors (TNFis), although the absolute risks seem low.

⇒ Due to the different mechanisms of actions of etanercept and other TNFis, the risk of demyelinating events may differ by the TNFi's mode of action.

WHAT THIS STUDY ADDS

⇒ We compared the risk of neuroinflammatory disorders in patients with rheumatoid arthritis, psoriatic arthritis or spondyloarthropathies treated with etanercept versus treated with TNFi with other modes of action and demonstrate that the incidence rates were similar for etanercept and for TNFi with other modes of action, but dissimilar across indications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The rheumatological diagnosis (rheumatoid arthritis vs psoriatic arthritis and spondyloarthropathies) but not the choice of specific TNFi plays an important role in the risk of neuroinflammatory events.

INTRODUCTION

Treatment with tumour necrosis factor alpha inhibitors (TNFis) is the mainstay for several rheumatic diseases, including rheumatoid arthritis (RA) and spondyloarthritis (SpA), the latter comprising psoriatic arthritis (PsA)

Table 1 Baseline characteristics of each treatment cohort (etanercept vs other TNFi) by country: patients with RA

	Denmark		Finland		Iceland		Norway		Sweden	
Treatment cohorts	Etanercept	oTNFi	Etanercept	oTNFi	Etanercept	oTNFi	Etanercept	oTNFi	Etanercept	oTNFi
Episodes, n	4968	9037	1923	3226	409	773	598	1168	13067	17535
Patients*, n	4486	6674	1411	2330	241	482	456	907	8274	11523
TNFi										
Adalimumab	0	3411	0	1640	0	265	0	200	0	6913
Certolizumab pegol	0	1485	0	342	0	<5	0	519	0	2019
Infliximab	0	3715	0	789	0	414	0	287	0	6805
Golimumab	0	426	0	455	0	92	0	162	0	1798
Female (%)	3777 (76)	6806 (75)	1459 (76)	2404 (75)	309 (76)	573 (74)	454 (76)	877 (75)	10163 (78)	13418 (77)
Age at TNFi start	57 (48–66)	57 (47–65)	54 (43–62)	54 (44–61)	52 (41–62)	52 (42–61)	55 (42–63)	55 (44–64)	58 (46–66)	58 (47–66)
Disease duration (years)										
<1	138 (3)	346 (4)	69 (4)	119 (4)	58 (17)	97 (15)	67 (14)	114 (12)	703 (5)	1044 (6)
1–5	1561 (33)	2902 (33)	487 (26)	780 (25)	145 (42)	267 (40)	158 (32)	266 (29)	3710 (29)	4758 (28)
>5	3097 (65)	5468 (63)	1343 (71)	2254 (71)	146 (42)	299 (45)	269 (54)	537 (59)	8472 (66)	11421 (66)
Number previous b/tsDMARDs										
0	2436 (49)	6094 (67)	1280 (67)	2149 (67)	233 (57)	476 (62)	336 (56)	629 (54)	7717 (59)	10848 (62)
1	1827 (37)	1913 (21)	539 (28)	686 (21)	138 (34)	169 (22)	185 (31)	324 (28)	3592 (27)	4159 (24)
2	498 (10)	683 (8)	89 (5)	292 (9)	29 (7)	88 (11)	59 (10)	130 (11)	1162 (9)	1604 (9)
3	144 (3)	241 (3)	14 (1)	69 (2)	6 (1)	27 (3)	15 (3)	61 (5)	419 (3)	626 (4)
4	63 (1)	106 (1)	1 (0)	30 (1)	3 (1)	13 (2)	3 (1)	24 (2)	177 (1)	298 (2)
Clinical measurements										
CRP	10.0 (4.0–25.0)	10.0 (4.0–25.0)	10.0 (5.0–26.0)	10.0 (5.0–29.0)	5.0 (3.0–17.0)	7.0 (3.0–17.0)	5.0 (2.0–13.0)	5.0 (2.0–13.0)	9.0 (4.0–24.0)	10.0 (4.0–27.0)
SJC	4 (1–7)	4 (2–8)	3 (1–7)	3 (1–7)	5 (2–8)	5 (2–10)	3 (1–6)	3 (1–6)	5 (2–9)	6 (3–10)
TJC	6 (3–12)	7 (3–12)	4 (1–7)	3 (1–7)	6 (2–10)	6 (3–11)	4 (1–8)	4 (1–9)	6 (2–10)	6 (3–10)
PGH	33 (20–50)	35 (20–51)	50 (26–69)	52 (29–70)	70 (50–84)	69 (50–82)	49 (26–70)	50 (28–70)	59 (39–75)	60 (40–75)
HAQ†	1.3 (0.8–1.8)	1.3 (0.8–1.8)	1.0 (0.5–1.5)	1.0 (0.5–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.6)	0.6 (0.3–1.0)	0.6 (0.3–1.0)	1.1 (0.6–1.5)	1.1 (0.8–1.6)
Pain VAS	62 (40–77)	60 (39–75)	50 (27–70)	53 (29–72)	65 (42–80)	67 (45–80)	47 (21–70)	42 (22–65)	60 (38–75)	60 (39–75)
DAS28	4.7 (3.7–5.6)	4.7 (3.7–5.6)	4.4 (3.4–5.4)	4.3 (3.2–5.3)	4.5 (3.6–5.2)	4.7 (3.8–5.6)	3.9 (3.0–4.8)	4.0 (3.0–4.8)	4.6 (3.7–5.4)	4.7 (3.8–5.5)
Concomitant methotrexate	2978 (60)	6339 (70)	708 (53)	1368 (61)	180 (44)	350 (45)	370 (62)	753 (64)	8198 (63)	12373 (71)
Comorbidities										
IBD	68 (1)	200 (2)	9 (0)	67 (2)	1 (0)	3 (0)	2 (0)	22 (2)	108 (1)	313 (2)
Diabetes	152 (3)	212 (2)	27 (1)	40 (1)	4 (1)	8 (1)	18 (3)	28 (2)	397 (3)	492 (3)
Thyroidea	279 (6)	447 (5)	47 (2)	73 (2)	6 (1)	4 (1)	24 (4)	39 (3)	622 (5)	742 (4)
Smoking										
Current	390 (8)	600 (7)	38 (2)	69 (2)	47 (11)	95 (12)	99 (17)	184 (16)	747 (6)	964 (5)

Continued

Table 1 Continued

	Denmark		Finland		Iceland		Norway		Sweden	
Former	420 (9)	603 (7)	9 (0)	14 (0)	102 (25)	180 (23)	206 (34)	352 (30)	2537 (19)	3039 (17)
Never	754 (15)	981 (11)	193 (10)	270 (8)	163 (40)	267 (35)	180 (30)	344 (29)	2294 (18)	2833 (16)
Missing	3404 (69)	6853 (76)	1683 (88)	2873 (89)	97 (24)	231 (30)	113 (19)	288 (25)	7489 (57)	10 699 (61)

Median (quartiles) for continuous variables and number (percentages) for binary variables are displayed. If not otherwise specified, the statistics pertain to treatment episodes. All variables are measured at treatment start.
*Patients were allowed starting a treatment with the same molecule several times.
†mHAQ in Norway.
b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CRP, C reactive protein (mg/L); DAS28, Disease Activity Score based on 28 joint count and CRP; HAQ, Health Assessment Questionnaire; IBD, inflammatory bowel disease; mHAQ, modified Health Assessment Questionnaire; oTNFi, other tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, infliximab, golimumab); PGH, patient's global health assessment; RA, rheumatoid arthritis; SJC, 28 swollen joint count; TJC, 28 tender joint count; TNFi, tumour necrosis factor inhibitor; VAS, 0–100 Visual Analogue Scale.

and axial and peripheral spondyloarthritis (AS/SpA).[1–3] Although rare, events of neuroinflammatory disorders, such as demyelinating disease (DML; including multiple sclerosis (MS)) and inflammatory polyneuropathies (IPN), have been reported in association with treatment with TNFis.[4–9]

Whether these neuroinflammatory events are causally linked to TNFi remains uncertain, although links between the specific mechanism of action of different TNFis and central nervous system demyelination have been described.[10–13] TNFis inhibit TNF-driven signalling by blocking the interactions between TNF molecules and their receptors. The two types of TNF, the transmembrane molecule TNF (tmTNF) and the soluble TNF (sTNF), are blocked by all TNFis, but etanercept is less effective than other TNFis in blocking tmTNF, while all are similarly effective with regard to inhibition of sTNF.[14–17] With regard to demyelination, tmTNF promotes mostly protective features such as cell survival and remyelination, while sTNF promotes inflammation.[10 12 13] Mice models have indicated that selective inhibition of sTNF may be therapeutic in autoimmune encephalomyelitis.[10] If the same would apply to humans, the association between TNFis and risk of neuroinflammatory events may therefore differ between etanercept, (which would be hypothesised to have no increased risk or even a protective effect), and TNFis with other modes of action (other TNFis (oTNFis)), (which would increase the risk).[14]

Since neuroinflammatory events are rare, most evidence on the safety of TNFi with respect to demyelinating events comes from case reports and smaller case series.[5 6 18–22] Comparative studies are sparse. In a study based on data from Sweden and Denmark, we showed that the incidence rates (IRs) of neuroinflammatory events in patients with RA were lower than the IRs in patients with SpA, and demonstrated that, in patients with SpA, being treated with TNF inhibitor was associated with an increased risk of neuroinflammatory events compared with not being treated with a biologic disease-modifying antirheumatic drug (bDMARD).[23] A study from Kunchok *et al*[24] suggested that this increased risk also applied to patients with RA.

To further investigate the (differential) association between the two types of TNFi drugs and neuroinflammatory events in patients with RA and SpA, this study aimed to contrast the risks with etanercept to those with four other TNFis.

METHODS

We performed an observational cohort study on the association between treatment with specific TNFi drugs (exposure) and risk of neuroinflammatory events (outcome). We used prospectively collected individual patient-level data from registers in Denmark, Finland, Iceland, Norway and Sweden during the study period from 1 January 2001 (1 January 2009 for Norway) through 1 October 2021 (1

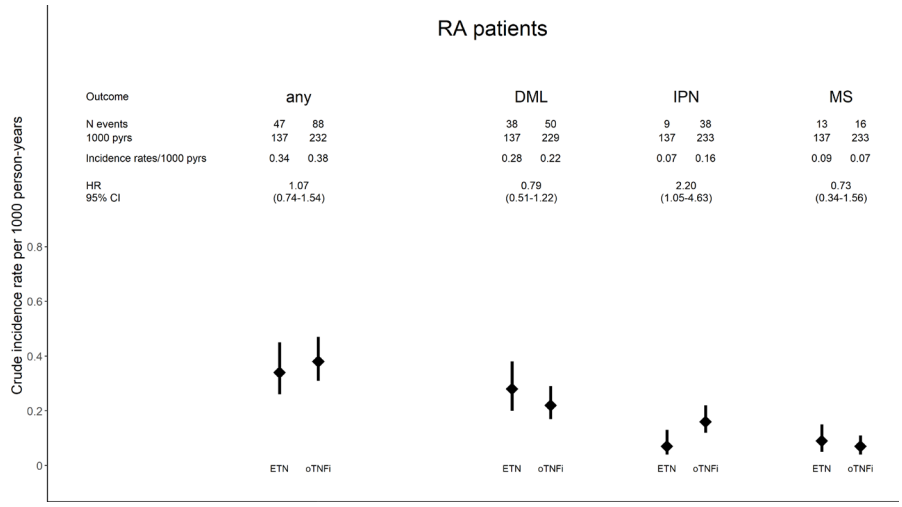

Figure 1 Number of events, person-years and crude incidence rates of neuroinflammatory events in patients with RA. The values of HR (95% CI) from the comparison of oTNFi with etanercept with Cox regression analyses are displayed. The analyses were adjusted for age, sex, calendar period of TNFi start, disease duration, CRP and concomitant use of methotrexate, and stratified by the number of b/tsDMARDs the patients had been exposed to prior to the TNFi start. Displayed HRs resulted from a random-effects meta-analysis of the analyses performed in Denmark (Danish data) and in Sweden (pooled data from Finland, Iceland, Norway and Sweden, with Cox regressions also stratified by country). 'Any' refers to any neuroinflammatory event (DML, IPN or MS). b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CRP, C reactive protein; DML, demyelinating disease; ETN, etanercept; IPN, inflammatory polyneuropathy; MS, multiple sclerosis; oTNFi: other tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, infliximab, golimumab); pyrs, person-years; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

January 2019 for Denmark, 31 May 2020 for Norway, 31 December 2020 for Sweden and Finland).

Design and setting

In the Nordic countries, healthcare systems are tax-funded; individual-level information on healthcare use is recorded in clinical and administrative registers. For this study, we identified patients with RA and those with SpA (here defined as PsA or AS/SpA) from the following clinical rheumatology registers (CRRs): DANBIO (Denmark), ROB-FIN (Finland), ICEBIO (Iceland), NOR-DMARD (Norway) and SRQ (the Swedish Rheumatology Quality Register, Sweden).[25–30] Using personal identification numbers assigned to all residents, data from these CRRs were linked to other health and population registers within each country. In brief, we used the National Patient Register in each country to identify past

Table 2 HR and 95% CI obtained from Cox regression comparing oTNFi with etanercept in patients with RA

	Etanercept n/1000 pyr	oTNFi n/1000 pyr	Country*	Model 1† HR (95% CI)	Model 2 ‡HR (95% CI)	Model 3§ HR (95% CI)	Meta-analysis HR (95% CI)
Outcome							
Any	47/137	88/232	Denmark	1.09 (0.51 to 2.31)	1.09 (0.52 to 2.32)	1.14 (0.54 to 2.42)	1.07 (0.74 to 1.54)
			FI, ICE, NO, SE, pooled	1.10 (0.73 to 1.66)	1.10 (0.73 to 1.66)	1.04 (0.68 to 1.59)	
DML	38/137	50/229	Denmark	0.80 (0.31 to 2.04)	0.78 (0.30 to 2.01)	0.82 (0.32 to 2.11)	0.79 (0.51 to 1.22)
			FI, ICE, NO, SE, pooled	0.78 (0.48 to 1.26)	0.79 (0.49 to 1.28)	0.78 (0.47 to 1.28)	
IPN	9/137	38/233	Denmark	1.79 (0.49 to 6.52)	1.78 (0.49 to 6.48)	1.83 (0.50 to 6.67)	2.20 (1.05 to 4.63)
			FI, ICE, NO, SE, pooled	2.77 (1.13 to 6.80)	2.73 (1.11 to 6.69)	2.41 (0.97 to 5.97)	
MS	13/137	16/233	Denmark	0.66 (0.20 to 2.18)	0.69 (0.21 to 2.27)	0.78 (0.24 to 2.54)	0.73 (0.34 to 1.56)
			FI, ICE, NO, SE, pooled	0.73 (0.28 to 1.90)	0.80 (0.31 to 2.08)	0.70 (0.26 to 1.88)	

The follow-up started at TNFi start and ended at first registered event date, emigration, death or end of the study period, whichever came first. Patients could be on any line of biological therapy.
All analyses were stratified by the number of previous biologic or targeted synthetic disease-modifying antirheumatic drugs (stratified Cox).
'Any' refers to any neuroinflammatory event (DML, IPN or MS).
*'FI, ICE, NO, SE, pooled' includes Finland, Iceland, Norway and Sweden: pooled data, analysis stratified by country (stratified Cox).
†Model 1: crude estimate.
‡Model 2: analyses were adjusted for age, sex and calendar year.
§Model 3: analyses were further adjusted for CRP, disease duration and concomitant methotrexate.
CRP, C reactive protein (mg/L); DML, demyelinating disease; IPN, inflammatory polyneuropathy; MS, multiple sclerosis; oTNFi, other tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, infliximab, golimumab); pyr, person-years; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

Table 3 Number of events, person-years, crude incidence rates (95% CL) and HR (95% CI) obtained from Cox regression comparing each TNFi with etanercept for the combined outcome (any neuroinflammatory event) and in patients with RA

	Events, n	Person-years	Crude incidence rates per 1000 person-years (95% CL)	Meta-analysis HR (95% CI)
TNFi				
Etanercept	47	137 135	0.34 (0.26–0.46)	Reference
Adalimumab	36	97 840	0.37 (0.27–0.51)	1.03 (0.65 to 1.62)
Certolizumab pegol	10	21 123	0.47 (0.25–0.88)	1.40 (0.68 to 2.90)
Golimumab	5	14 289	0.35 (0.15–0.84)	1.08 (0.37 to 3.16)
Infliximab	36	98 468	0.37 (0.26–0.51)	1.06 (0.67 to 1.70)

CL, confidence limits; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

and incident neuroinflammatory events and comorbidities, and the population registers for emigration and vital status of the patients.[31]

Exposure definition

In the CRRs, we identified all registered TNFi treatment initiations. We made no distinction between a biosimilar and its originator product, and we disregarded any treatment interruption of the same TNFi shorter than 3 months. At each treatment start, the number of biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) the patient had been previously exposed to was retrieved. Treatment initiations preceded by more than four b/tsDMARD exposures were excluded. We defined two exposure cohorts: initiators of etanercept and initiators of any other TNFi, respectively. One patient could contribute to more than one cohort (eg, a patient starting etanercept, later switching to adalimumab, before switching to infliximab, contributed with one observation to the etanercept cohort and two observations to the oTNFi cohort). Patients were excluded if at treatment start they had a history of any neuroinflammatory event. Only treatments started during the study period were analysed.

Outcome

We defined three groups of neuroinflammatory events using the 10th version of the International Classification of Diseases (ICD-10), together with a fourth definition combining the following three (ie, having at least one of them): (1) demyelinating events (DML), including DML of the central nervous system and optic neuritis (ICD-10 G35, G36.0, G36.8, G36.9, G37.1, G37.3, G37.5, G37.8, G37.9, G04.8, G04.9, H46 and H48.1); (2) IPN, including inflammatory and drug-induced polyneuropathies (ICD-10 G61.0, G61.8 and G61.9); and (3) MS (ICD-10 G35; also included in DML). For each treatment cohort, the first registration with any of the neuroinflammatory outcome diagnosis codes was retrieved from the National Patient Register, recorded as main or secondary diagnosis in outpatient care or hospitalisation.

Statistical analyses

Main analysis

We performed separate analyses for patients with RA and patients with SpA. In each indication, the two TNFi exposure cohorts (etanercept vs oTNFi) were followed from treatment start until the end of follow-up. We applied an 'ever since treatment start' approach in which follow-up ended at the first registered neuroinflammatory event (the one under investigation), emigration, death or end of the study period, whichever came first, hence disregarding treatment discontinuation or switch to another drug. For example, an event occurring during treatment with the second TNFi treatment initiated during follow-up would be attributed to both TNFi treatment courses during the study period. For each exposure and indication, we calculated the number of neuroinflammatory events, the follow-up time at risk and the crude IRs. Separately for each indication, we compared the incidences with oTNFi and etanercept, using the latter as reference, and obtained the HR and the 95% CI using Cox regressions, with time since treatment start as the time scale, and a robust sandwich estimator to account for the correlated data structure. All analyses were stratified by the number of b/tsDMARDs the patients had been exposed to prior to the TNFi start. In addition to an unadjusted model (model 1), we performed analyses adjusted for age, sex and calendar period of TNFi start (model 2), and further adjusted for disease duration, C reactive protein (CRP) and concomitant use of methotrexate (model 3). All included covariates were chosen a priori and intended to capture important potential confounders such as demographics (age, sex), time trends (calendar year), level and duration of inflammation (CRP and disease duration), and comedication (methotrexate). CRP at treatment start was categorised into quartiles with a 'missing' category added to these. No imputation was performed for other variables. Each variable was measured at treatment start and retrieved from the CRR. The Danish data were analysed in Denmark, as individual-level data from the Danish national health registers can only be analysed in Denmark due to data security policy. The data from the four other countries

Table 4 Baseline characteristics of each treatment cohort (etanercept vs other TNFi) by country: patients with SpA

	Denmark		Finland		Iceland		Norway		Sweden	
Treatment cohorts	Etanercept	oTNFi	Etanercept	oTNFi	Etanercept	oTNFi	Etanercept	oTNFi	Etanercept	oTNFi
Episodes, n	3175	9208	1244	2739	366	1231	1018	2731	8581	16279
Patients*, n	2896	6140	946	1928	144	818	713	1980	5440	9803
TNFi										
Adalimumab	0	3552	0	1341	0	367	0	617	0	7114
Certolizumab pegol	0	924	0	175	0	<5	0	870	0	1291
Infliximab	0	3280	0	661	0	717	0	576	0	5261
Golimumab	0	1452	0	562	0	145	0	668	0	2613
Female (%)	1632 (51)	4303 (47)	559 (45)	1143 (42)	216 (59)	616 (50)	506 (50)	1387 (51)	4431 (52)	7844 (48)
Age at TNFi start	45 (35–54)	43 (34–53)	44 (34–54)	45 (35–53)	47 (37–55)	45 (35–55)	43 (34–53)	44 (36–54)	47 (36–57)	45 (35–55)
Disease duration (years)										
<1	349 (12)	1384 (16)	52 (5)	153 (6)	69 (21)	345 (33)	197 (26)	397 (21)	496 (6)	867 (5)
1–5	1293 (44)	3407 (40)	371 (33)	810 (32)	115 (35)	296 (28)	214 (29)	520 (27)	2069 (24)	3745 (23)
>5	1306 (44)	3725 (44)	700 (62)	1531 (61)	140 (43)	410 (39)	334 (45)	979 (52)	5937 (70)	11507 (71)
Number of previous b/tsDMARDs										
0	1467 (46)	5978 (65)	885 (71)	1820 (66)	143 (39)	817 (66)	579 (57)	1447 (53)	5312 (62)	9650 (59)
1	1240 (39)	1809 (20)	311 (25)	565 (21)	175 (48)	252 (20)	301 (30)	742 (27)	2259 (26)	3829 (24)
2	351 (11)	869 (9)	36 (3)	262 (10)	35 (10)	114 (9)	101 (10)	345 (13)	655 (8)	1765 (11)
3	97 (3)	394 (4)	9 (1)	74 (3)	11 (3)	38 (3)	26 (3)	137 (5)	253 (3)	743 (5)
4	20 (1)	158 (2)	3 (0)	18 (1)	2 (1)	10 (1)	11 (1)	60 (2)	102 (1)	292 (2)
Clinical measurements										
CRP	5.0 (2.0–14.3)	6.0 (2.0–16.0)	8.0 (3.0–20.0)	7.0 (3.0–19.0)	4.0 (2.0–10.0)	6.0 (3.0–14.0)	5.0 (2.0–11.0)	5.0 (2.0–10.0)	5.0 (2.0–14.0)	6.0 (2.0–17.0)
SJC	0 (0–2)	0 (0–2)	1 (0–2)	1 (0–2)	2 (0–5)	1 (0–4)	0 (0–1)	0 (0–1)	1 (0–3)	0 (0–3)
TJC	2 (0–7)	2 (0–6)	1 (0–3)	1 (0–3)	3 (0–6)	2 (0–5)	0 (0–3)	1 (0–3)	2 (0–6)	2 (0–6)
PGH	28 (15–45)	29 (15–45)	51 (25–70)	50 (25–70)	70 (48–82)	70 (50–83)	57 (37–74)	54 (35–72)	62 (44–76)	62 (43–77)
HAQ†	1.0 (0.6–1.5)	1.0 (0.6–1.5)	0.8 (0.3–1.4)	0.8 (0.4–1.3)	1.0 (0.6–1.5)	0.9 (0.5–1.4)	0.6 (0.3–0.9)	0.6 (0.3–0.9)	0.9 (0.5–1.3)	0.9 (0.5–1.3)
Pain VAS	66 (46–81)	66 (47–80)	55 (30–71)	55 (30–72)	66 (44–80)	67 (47–79)	53 (32–71)	51 (31–70)	63 (44–76)	63 (43–77)
BASDAI	6.4 (4.8–7.7)	6.3 (4.8–7.7)	4.1 (1.8–6.2)	4.2 (2.0–5.9)	6.5 (5.8–8.1)	6.1 (4.5–7.6)	5.3 (3.4–6.8)	5.0 (3.2–6.6)	5.8 (4.1–7.1)	5.8 (4.1–7.2)
ASDAS	3.5 (2.8–4.1)	3.4 (2.7–4.1)	2.9 (2.1–3.7)	2.8 (1.9–3.5)	3.3 (2.7–4.2)	3.5 (2.9–4.0)	2.9 (2.3–3.7)	2.9 (2.2–3.6)	3.1 (2.4–3.8)	3.2 (2.4–3.8)
Concomitant methotrexate	979 (31)	3042 (30)	369 (44)	949 (52)	92 (25)	292 (24)	228 (22)	734 (27)	3266 (38)	6805 (42)
Comorbidities										
IBD	102 (3)	487 (5)	21 (2)	164 (6)	4 (1)	35 (3)	15 (1)	164 (6)	235 (3)	1420 (9)
Diabetes	53 (2)	128 (1)	9 (1)	15 (1)	2 (1)	9 (1)	13 (1)	37 (1)	124 (1)	225 (1)
Thyroidea	113 (4)	243 (3)	17 (1)	30 (1)	1 (0)	6 (0)	12 (1)	49 (2)	238 (3)	365 (2)

Continued

Table 4 Continued

	Denmark	Finland		Iceland	Norway		Sweden	
Smoking								
Current	349 (11)	906 (10)	25 (2)	100 (4)	57 (16)	184 (15)	196 (19)	501 (18)	571 (7)	1164 (7)
Former	240 (8)	495 (5)	8 (1)	33 (1)	86 (23)	198 (16)	286 (28)	774 (28)	1719 (20)	3241 (20)
Never	492 (16)	1249 (14)	105 (8)	348 (13)	129 (35)	426 (35)	361 (35)	931 (34)	2096 (24)	3957 (24)
Missing	2094 (66)	6558 (71)	1106 (89)	2258 (82)	94 (26)	423 (34)	175 (17)	525 (19)	4195 (49)	7917 (49)

Median (quartiles, IQR) for continuous variables and number (percentages) for binary variables are displayed. If not otherwise specified, the statistics pertain to treatment episodes. All variables are measured at treatment start.
*Patients were allowed starting a treatment with the same molecule several times.
†mHAQ in Norway.
ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CRP, C reactive protein (mg/L); HAQ, Health Assessment Questionnaire; IBD, inflammatory bowel disease; mHAQ, modified Health Assessment Questionnaire; oTNFi, other tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, infliximab, golimumab); PGH, patient's global health assessment; SJC, 28 swollen joint count; SpA, spondyloarthritis (including psoriatic arthritis and ankylosing spondylitis); TJC, 28 tender joint count; TNFi, tumour necrosis factor inhibitor; VAS, 0–100 Visual Analogue Scale.

were pooled and analysed in Sweden where the Cox regressions were also stratified by country. Cox regression results for the five countries together were estimated from a random-effects meta-analysis of the latter and the Danish results. In all tabulations, cells with less than five neuroinflammatory events are displayed as 'n/a' and no HRs were assessed. Data analyses were performed in SAS V.9.4, and figures were obtained in R V.4.2.0 (ggplot2 package).

Secondary analyses

We performed the analyses splitting the four drugs (adalimumab, certolizumab pegol, infliximab and golimumab) that had been previously grouped together as oTNFi. We also performed the analyses separately for PsA and AS/SpA.

Sensitivity analyses

For testing the robustness of our results, we performed several sensitivity analyses by (1) applying an 'on-drug' approach in which, in addition to the censoring events described above, we ended follow-up 3 months after each treatment discontinuation; (2) performing the analyses in patients where the TNFi was their first ever b/tsDMARD therapy; (3) starting the follow-up 3 months after treatment start in order to avoid attributing an event to the starting treatment should the first symptoms appeared just around the treatment start; and (4) stratifying the follow-up time (less than 1 year, 1–5 years, more than 5 years) for investigating any time structure in the occurrence of events.

Data protection and data sharing

Data from Finland, Iceland, Norway and Sweden are available on reasonable request, but access is regulated by the legal framework of the register linkages performed; Danish data are not available.

Patient involvement

This study was performed within the context of a Nordic rheumatology registers collaboration, which employed a patient representative panel which was not directly involved in the design and conduct of this study.

RESULTS

Rheumatoid arthritis

The study included 33 883 patients with RA initiating 52 704 treatment courses with a TNFi (76% women, mean age 55 (SD 13) years). Denmark contributed 14 005 treatment courses, Finland 5149, Iceland 1182, Norway 1766 and Sweden 30 602. Of these, 61% represented a first ever b/tsDMARD start. Etanercept represented 41% of all treatment courses (table 1). In each country, the characteristics of the patients in the two treatment groups were overall similar for all measured variables.

During 369 505 person-years, we observed a total of 135 incident neuroinflammatory events corresponding to a crude IR of 0.37 per 1000 person-years, 0.34 for

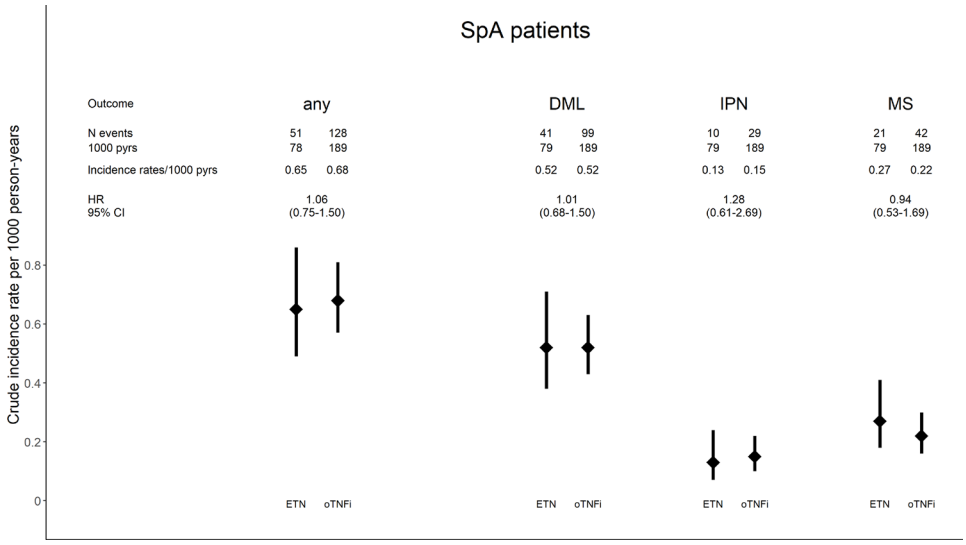

Figure 2 Number of events, person-years and crude incidence rates of neuroinflammatory events in patients with SpA. The values of the HR (95% CI) from the comparison of oTNFi with etanercept with Cox regression analyses are displayed. The analyses were adjusted for age, sex, calendar period of TNFi start, disease duration, CRP and concomitant use of methotrexate, and stratified by the number of b/tsDMARDs the patients had been exposed to prior to the TNFi start. Displayed HRs resulted from a random-effects meta-analysis of the analyses performed in Denmark (Danish data) and in Sweden (pooled data from Finland, Iceland, Norway and Sweden, with Cox regressions also stratified by country). 'Any' refers to any neuroinflammatory event (DML, IPN or MS). b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CRP, C reactive protein; DML, demyelinating event; ETN, etanercept; IPN, inflammatory polyneuropathy; MS, multiple sclerosis; oTNFi, other tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, infliximab, golimumab); pyrs, person-years; SpA, spondyloarthritis (including psoriatic arthritis and ankylosing spondylitis); TNFi, tumour necrosis factor inhibitor.

etanercept and 0.38 for oTNFi. The number of DML, IPN and MS events was 88, 47 and 29, respectively; thus, DML represented 65% of the total number of events, of which 33% were MS (figure 1).

Table 2 displays the crude and successively adjusted HRs resulting from the comparison of oTNFi with etanercept by outcome. The meta-analysis of the results obtained in Denmark and in Sweden (for the Finnish, Icelandic, Norwegian and Swedish pooled data) provided an HR of 1.07 (95% CI 0.74 to 1.54) for the combined outcome of all neuroinflammatory events with oTNFi versus etanercept. For the specific outcomes, the corresponding HRs were 0.79 (95% CI 0.51 to 1.22) for DML, 2.2 (95% CI 1.05 to 4.63) for IPN and 0.73 (95% CI 0.34 to 1.56) for MS.

Secondary analysis: individual TNFis

When analysing individual TNFis, we did not observe strong variations between crude IRs of the combined outcome, with the lowest for etanercept (0.34 (0.26–0.46) per 1000 person-years) and the highest for certolizumab pegol (0.47 (0.25–0.88); table 3). For the specific outcomes, modelling individual TNFis (with etanercept as reference) was only possible for the comparison of adalimumab and infliximab with etanercept and was performed without Danish data (which included too few events). Regarding IPN, we obtained an HR of 1.88 (0.65–5.47) for adalimumab and 3.04 (1.05–8.79) for infliximab (vs etanercept). For DML and MS, all HRs were close to 1 (data not shown).

Spondyloarthritis

The study included 28 772 patients with SpA initiating 46 572 treatment courses with a TNFi (49% women, mean age 45 (SD 13) years). Denmark contributed 12 383 treatment courses, 3983 from Finland, 1597 from Iceland, 3749 from Norway and 24 860 from Sweden. Sixty per cent represented a first ever b/tsDMARD start. Etanercept represented 33% of all treatment courses. For the characteristics, see table 4.

During 267 314 person-years, we observed a total of 179 incident neuroinflammatory events, corresponding to a crude IR of 0.67 per 1000 person-years, 0.65 for etanercept vs 0.68 for oTNFi. The number of DML, IPN and MS events was 140, 39 and 63, respectively, with DML representing 78% of the total number of events, with 45% of these being MS (figure 2).

The HR for the comparison of oTNFi with etanercept, by outcome, through the meta-analysis of the results obtained from analyses performed in Denmark and in Sweden, was 1.06 (95% CI 0.75 to 1.50) for oTNFi versus etanercept for the combined outcome of all neuroinflammatory events. For the specific outcomes, the corresponding HRs were 1.01 (95% CI 0.68 to 1.50) for DML, 1.28 (95% CI 0.61 to 2.69) for IPN and 0.94 (95% CI 0.53 to 1.69) for MS (table 5).

Secondary analyses

Separate analyses in subgroups of patients defined by indication (PsA vs AS/SpA) for all neuroinflammatory events revealed that crude IRs were higher in AS/SpA

Table 5 HR and 95% CI obtained from Cox regression comparing oTNFi with etanercept in patients with SpA

	Etanercept n/1000 pyr	oTNFi n/1000 pyr	Country*	Model 1† HR (95% CI)	Model 2‡ HR (95% CI)	Model 3§ HR (95% CI)	Meta-analysis HR (95% CI)
Outcome							
Any	51/78	128/189	Denmark	0.74 (0.38 to 1.45)	0.75 (0.38 to 1.46)	0.95 (0.47 to 1.94)	1.06 (0.75 to 1.50)
			FI, ICE, NO, SE, pooled	1.08 (0.74 to 1.57)	1.09 (0.74 to 1.59)	1.09 (0.73 to 1.63)	
DML	41/79	99/189	Denmark	0.65 (0.28 to 1.53)	0.65 (0.28 to 1.54)	0.98 (0.37 to 2.55)	1.01 (0.68 to 1.50)
			FI, ICE, NO, SE, pooled	1.01 (0.67 to 1.53)	1.03 (0.68 to 1.55)	1.01 (0.65 to 1.57)	
IPN	10/79	29/189	Denmark	0.91 (0.31 to 2.65)	0.91 (0.31 to 2.67)	0.97 (0.33 to 2.89)	1.28 (0.61 to 2.69)
			FI, ICE, NO, SE, pooled	0.87 (0.48 to 1.59)	0.91 (0.50 to 1.65)	1.00 (0.53 to 1.91)	
MS	21/79	42/189	Denmark	0.38 (0.12 to 1.17)	0.37 (0.12 to 1.14)	0.71 (0.18 to 2.81)	0.94 (0.53 to 1.69)
			FI, ICE, NO, SE, pooled	1.49 (0.55 to 4.09)	1.52 (0.55 to 4.17)	1.63 (0.59 to 4.49)	

The follow-up started at TNFi start and ended at first registered event date, emigration, death or end of the study period, whichever came first. Patients could be on any line of biological therapy.
All analyses were stratified by the number of previous biologic or targeted synthetic disease-modifying antirheumatic drugs (stratified Cox).
'Any' refers to any neuroinflammatory event (DML, IPN or MS).
*'FI, ICE, NO, SE, pooled' includes Finland, Iceland, Norway and Sweden: pooled data, analysis stratified by country (stratified Cox).
†Model 1: crude estimate.
‡Model 2: analyses were adjusted for age, sex and calendar year.
§Model 3: analyses were further adjusted for CRP, disease duration and concomitant methotrexate.
CRP, C reactive protein (mg/L); DML, demyelinating disease; IPN, inflammatory polyneuropathy; MS, multiple sclerosis; oTNFi, other tumour necrosis factor inhibitors (adalimumab, certolizumab pegol, infliximab, golimumab); pyr, person-years; SpA, spondyloarthritis (including psoriatic arthritis and ankylosing spondylitis); TNFi, tumour necrosis factor inhibitor.

than in PsA, respectively, 0.79 and 0.52 per 1000 person-years, but for both indications the rates with etanercept did not differ significantly from those of oTNFi (online supplemental table 1).

When analysing individual TNFis, the crude IRs of all neuroinflammatory events ranged from 0.60 (0.44–0.82) per 1000 person-years for infliximab to 0.82 (0.46–1.49) for certolizumab pegol (table 6). Analyses of specific neuroinflammatory outcomes were performed without Danish data, which included too few events, and provided HRs that were either close to 1 or uninterpretable due to large CIs (data not shown).

Sensitivity analyses

The three sensitivity analyses (applying an 'on-drug' approach, selecting patients on their first ever TNFi and starting the follow-up with a 3-month delay) had minor impact on the HRs (online supplemental table 2). Stratifying the follow-up time (less than 1 year, 1–5 years, more than 5 years) did not reveal any clear heterogeneity in the crude IRs over time, the comparison of the IRs should take the low number of events into account. (online supplemental table 3).

DISCUSSION

In this study, including more than 60 000 patients with RA or SpA from the five Nordic countries and almost 100 000 treatment episodes of TNFis, we did not observe any statistical difference in the rates of neuroinflammatory events by type of TNFi drug, although among the eight combinations of outcome types and treatment indications under study a higher rate of IPN with oTNFi versus etanercept was observed in patients with RA (but not in SpA).

We hypothesised that etanercept could differ from the other TNFis in the association with neuroinflammatory disorders since its inhibitory effect on TNF molecules differs from that of other TNFis. Etanercept has been shown to be less effective than the other TNFis in blocking tmTNF, involved in remyelination, while all TNFis are similarly effective in blocking sTNF, which

Table 6 Number of events, person-years, crude incidence rates (95% CL) and HR (95% CI) obtained from Cox regression comparing each TNFi with etanercept for the combined outcome (any neuroinflammatory event) and in patients with SpA

	Events, n	Person-years	Crude incidence rates per 1000 person-years (95% CL)	Meta-analysis HR (95% CI)
TNFi				
Etanercept	51	78 390	0.65 (0.49–0.86)	Reference
Adalimumab	58	81 436	0.71 (0.55–0.92)	1.07 (0.71 to 1.60)
Certolizumab pegol	11	13 363	0.82 (0.46–1.49)	1.36 (0.64 to 2.91)
Golimumab	19	26 930	0.71 (0.45–1.11)	1.16 (0.64 to 2.09)
Infliximab	40	66 629	0.60 (0.44–0.82)	0.98 (0.62 to 1.55)

CL, confidence limits; SpA, spondyloarthritis (including psoriatic arthritis and ankylosing spondylitis); TNFi, tumour necrosis factor inhibitor.

promotes inflammation.[14–16] However, our results did not highlight any clear evidence of any clinically meaningful difference in risk with oTNFi than with etanercept. Comparative studies in this field have used TNFi treatment as one group.[23 24] Case and small series reports have presented individual TNFis separately but have been solely descriptive and without any comparator.[32] Thus, and to our knowledge, this is the first study to address the comparison of rates of demyelinating events by type of TNFi.

Aside from comparing etanercept with oTNFi, we also compared each individual TNFi, without observing any signal for a particular drug for all neuroinflammatory events, although for IPN and in RA only infliximab was associated with a threefold increased rate compared with etanercept, although with a large CI. Indeed, the finding of an increased risk for IPN in RA, but not in SpA, was unexpected and to our knowledge has not been previously reported. Our IPN definition included the ICD-10 code G61.9, that is, unspecified IPN, which may have inflated the number of events, which could be reported more often in patients treated for more severe RA, and for this reason preferably treated with infliximab compared with etanercept, and thus by nature not necessarily confined to drug-induced events.[33] Either way, this finding, based on few events, calls for replication.

Consistent with our previous findings and that of others, the crude rates of demyelinating events were higher in patients with SpA compared with patients with RA.[23 34 35] Interestingly, however, the relative risks for etanercept versus oTNFi did not differ substantially by indication. Previous studies have shown an inverse association between RA and MS,[36] while patients with psoriasis disease have been shown to be at higher risk for MS.[37] Also, the age distributions in patients with RA versus SpA differ substantially (the latter around a decade younger than the former), and MS generally occurs sooner in the course of life than RA (also around a decade). In our data, the mean age of onset of MS was around 45 years of age for both patients with RA and patients with SpA. The differences in both age distributions and the genetics between patients with RA and patients with SpA might explain the lower incidence of neuroinflammatory (at least MS) events in RA compared with SpA.[38]

Neuroinflammatory outcomes are relatively rare events, around 100 times less common than, for example, hospitalisation due to infection,[39] or around 8–10 times rarer than cardiovascular diseases.[40 41] This represents a challenge to studying factors involved in the occurrence of such outcomes. Nevertheless, among the analyses that we could perform on individual drugs, none provided HRs that would suggest any of the TNFi drugs to be more (or less) associated to DML or MS than etanercept.

Our study has limitations. One single recorded visit with an outcome-defining ICD code was used to define each outcome. This may leave room for misclassification, also between each individual type of neuroinflammatory events.[42] However, this would impact the IRs rather than the HRs as we have little reason to believe that such misclassification would differ between etanercept and oTNFi. We adjusted for a series of potential confounders, including age, sex, calendar year, disease duration, CRP and concomitant methotrexate, which did not substantially alter the estimates; however, we could not adjust for smoking status, which was characterised by a high percentage of missing values. In the event that smoking status differs between individual TNFi drugs, residual confounding may remain. We used data from a long calendar period, with a study period starting in 2001 when all drugs were not yet available. However, adjusting for calendar year in the analysis did not substantially change the results. All patients were free of neuroinflammatory disease at treatment start, but we did not have access to family history of such diseases. This study investigated a hypothesis regarding interdrug differences between individual TNF inhibitors. For this reason, we did not include data on non-TNFi bDMARD or tsDMARD treatment episodes. We also lack a comparator group from the general population, which would help to anchor our results. Data for MS in Sweden show that, at the mean age of our patients and taking the sex distribution into account, the IR of MS never exceeds 0.20 per 1000 person-years, which is less than the rate we observed in patients with SpA but higher than the rate in patients with RA.[43] We combined data from several countries and verified that there was no significant heterogeneity between these, yet care should be taken in generalising our results to all patients with RA or SpA.

Our study has several strengths. We were able to collect a large number of patients with RA and SpA, and a large number of treatment courses, making this study among the largest on this topic. This allowed us to assess the risk of neuroinflammatory disorders by type of outcome, by type of treated condition and by type of TNFi drug. In addition, patients were followed for a long time; the median follow-up was between 5 and 6 years, which ensures sufficient time for observing rare events. The use of register data also ensured low risk of (differential) misclassification of exposure, outcomes and covariates. Further, we could investigate the robustness of our results through sensitivity and secondary analyses, which did not show any signal that contradicted our main results.

In conclusion, the IRs of neuroinflammatory events were higher in SpA as compared with RA, all between 1/10 000 and 1/1000 person-years. However, the choice of specific TNFi drug does not seem to play an important role in the risk of neuroinflammatory events.

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