

Demyelinating Events Following Initiation of Anti-TNF α Therapy in the British Society for Rheumatology Biologics Registry in Rheumatoid Arthritis

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Abstract

Objective

To establish the incidence of demyelination in patients who have received anti-tumor necrosis factor alpha (anti-TNF α) therapy, through analysis of adverse events reported in a prospective cohort of patients receiving biological therapies.

Methods

A cohort study was performed on prospectively acquired data via the British Society for Rheumatology Biologics Register in Rheumatoid Arthritis. All potential demyelinating events during follow-up were extracted and classified as definite, probable, or possible blinded to treatment data. The point of starting an anti-TNF therapy in individuals with no prior reported demyelination was the time of exposure. Crude rates of demyelination and standardized incident rates (SIRs) compared with the general UK population were calculated.

Results

Thirty-five individuals with demyelinating events were identified from a total pool of 13,489. The median age at study entry was 44 years, and the median disease duration was 8 years; 71% were female. Events occurred a median of 3 (interquartile range 1–5) years from the start of the first anti-TNF therapy. Twenty-six events occurred in individuals still taking anti-TNF α therapy; of the other 9, 6 were within 90 days of drug withdrawal. The raw incidence of demyelination was 19.7/100,000 patient-years (95% CI 13.7–27.3). The SIR in the whole population was 1.38 (95% CI 0.96–1.92) and 0.83 (0.51–1.26) limited to definite/probable cases.

Conclusions

Demyelination following anti-TNF therapy is uncommon. Patients receiving anti-TNF α therapy show a marginally increased SIR; this is lost in sensitivity analyses. Patients concerned about anti-TNF α -associated demyelination can be relatively reassured by these data.

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Glossary

csDMARD = conventional synthetic disease-modifying antirheumatic drug; **IQR** = interquartile range; **MS** = multiple sclerosis; **pyears** = person-years; **RA** = rheumatoid arthritis; **SIR** = standardized incident rate; **TNF α** = tumor necrosis factor alpha.

Anti-tumor necrosis factor alpha (anti-TNF α) monoclonal antibodies are used to treat a number of autoimmune diseases, including rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, and uveitis. Approved anti-TNF α therapies include etanercept (a decoy TNF receptor protein) and adalimumab, infliximab, certolizumab, and golimumab (monoclonal antibodies directed against TNF α). As a class, anti-TNF α therapies have been associated with de novo CNS demyelination.¹ A clinical trial of lenercept, a recombinant TNF receptor p55 immunoglobulin fusion protein with a biological action of TNF- α blockade in multiple sclerosis (MS), failed to reach its primary MRI-based end point.² Concerningly, an increased relapse rate was seen early in the lenercept group with more severe neurologic deficits in the lenercept-treated group compared with placebo.²

The pathophysiologic relationship between tumor necrosis factor and MS is complex. *rs1800693*, a single nucleotide polymorphism in the *TNFRSF1A* gene, which encodes tumor necrosis factor receptor 1, has been implicated as a causal variant in the development of MS.³ The MS risk allele appears to lead to the expression of a soluble form of tumor necrosis factor receptor 1, which blocks TNF. It has been hypothesized that anti-TNF α therapies have an impact on MS risk via this mechanism; however, direct evidence supporting this hypothesis is lacking.

Despite the lack of direct evidence, there remain significant concerns around the use of anti-TNF α therapies in some patients. Some patients in whom anti-TNF α therapy is being considered may be referred to neurologists for assessment of the risk of demyelination, particularly those with neurologic symptoms or a family history of MS. Evaluating this risk is highly complex, with little data to inform risk-benefit discussions. Performing screening MRI on all patients considering anti-TNF α therapy is not feasible from a resource perspective, and the use of MRI in this way confers a risk of significant anxiety in patients as a result of incidental diagnoses with varying degrees of clinical significance being revealed.⁴

The British Society for Rheumatology Biologics Register in Rheumatoid Arthritis (BSRBR-RA) is a large, prospective pharmacovigilance study that aims to monitor the safety of anti-TNF α in patients with RA and related conditions.⁵ To date, more than 20,000 patients started on biologic therapy have been enrolled in the register. It thus provides a prospectively collected resource, enabling the study of rare adverse events occurring on or subsequent to anti-TNF α therapy. We set out to describe the characteristics and incidence of demyelination in patients who have received anti-

TNF α therapy to better inform both patients and clinicians and enable evidence-based decision making.

Methods

Case Identification

The study population comprised patients recruited to the BSRBR-RA, a prospective observational cohort study, up to November 30, 2019. Full methods have previously been described in detail.⁶ Briefly, baseline data (with baseline defined as at the time of starting a biological agent) are recorded by the treating rheumatologist or clinical research nurse using a standardized questionnaire. Data collected include demographics (age and sex), rheumatologic disease status (disease duration, joint counts, disease activity score 28,⁷ Health Assessment Questionnaire),⁸ disease indication, drug history, and comorbidities. Any prior history of demyelination at study registration is also recorded. Follow-up data are collected 6-monthly for the first 3 years following enrollment and annually thereafter, regardless of subsequent treatment changes. Follow-up data include current treatments, changes to antirheumatic therapy, and occurrence of serious and nonserious adverse events, including demyelination. All adverse events are reported verbatim by clinicians and coded centrally using the Medical Dictionary for Regulatory Activities.⁹ The BSRBR-RA is also linked to the mandatory national death register and is informed of any death and cause of death in patients registered in the study.

To be eligible for the current study, patients were required to have baseline registration with the BSRBR-RA at the time of starting an anti-TNF α therapy, have at least one 6-monthly follow-up recorded after registration, and have no known history of demyelination before registration. Patients entered into the BSRBR-RA with primary diagnoses other than RA, such as psoriatic arthritis, were included. All individual subject-level records meeting the above criteria were searched using both the Medical Dictionary for Regulatory Activities preferred terms and free-text event descriptions related to demyelination (search terms given in table e-1, links.lww.com/NXI/A467). All records identified using these search terms were retrieved, and the available clinical records reviewed.

Cases of incident demyelination were defined as any reported adverse event of demyelination in patients with no previous history of demyelination recorded at baseline. Demyelinating events affecting the CNS were categorized using available clinical information, blinded to underlying rheumatologic

diagnosis, anti-TNF α therapy subtype, and start/stop date, by a consultant neurologist specializing in neuroinflammation/MS (R.D.). Demyelinating events of interest were defined as those involving the CNS, including the spinal cord and optic nerve. Peripheral demyelinating events, such as chronic inflammatory demyelinating polyneuropathy, CIDP, and Guillain-Barre syndrome/acute inflammatory demyelinating polyneuropathy, AIDP, were excluded. Where available, brain and spine MRI reports and the results of neurophysiologic investigations were included in the review of clinical information, although the absence of data was not assumed to mean investigations were normal. Events were classified as definite MS, definite demyelination (but not meeting diagnostic criteria for MS), probable demyelination, and possible demyelination based on a framework informed by MacDonald 2017 criteria.¹⁰

Statistical Methods

For all patients, person-years (pyears) of exposure started from the date of the first treatment with the respective drug and continued until the first demyelinating event, most recent study follow-up (recorded up to November 30, 2019), or death, whichever came first. Events were only included if they occurred subsequent to anti-TNF α therapy initiation but events after the last dose of anti-TNF α , including those on subsequent therapies, were also included.

Characteristics of those patients who went on to develop a demyelinating event were described. Crude rates of demyelinating events are presented per 1,000 pyears with 95% CIs. Standardized incidence rates (SIRs) of events per 100,000 population compared with English population data based on Hospital Episode Statistics and General Practice Research Datalink data from 1997 to 2010 are also included.¹¹ As no population data were available after 2010, the same data from 2010 were used for subsequent years. A sensitivity analysis to determine SIRs only including events classified as probable or definite demyelination was performed, and exploratory analysis included only the population with RA.

All analyses were performed using Stata, version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Data Availability

This study analyzed existing data owned by and subject to license restrictions by the British Society for Rheumatology. Data sets are available through application to the BSR. All proposals for access are assessed by the steering committee. To access data, please email bsrbr@rheumatology.org.uk.

Standard Protocol Approvals, Registrations, and Patient Consents

The BSRBR-RA holds ethical approval from the Multicentre Research Ethics Committee for the North West of England (ref MREC 00/8/053). Written informed consent is obtained from all patients.

Results

Population Characteristics

Thirty-five individuals with demyelinating events were identified from a total eligible study population of 13,489 individuals with 172,107 pyears of follow-up data available. The baseline characteristics and characteristics at the time of the initial report of demyelinating event of these 35 individuals are detailed in tables 1 and 2.

Seventy-one percent of patients who developed demyelination had a baseline diagnosis of RA, 14% ankylosing spondylitis, and 5% psoriatic arthritis (table 1). The median age at BSRBR-RA registration was 44 years (interquartile range [IQR] 37–57 years), and the median age at demyelinating event was 50 years (IQR 43–59 years); 71% were female. The median disease duration at demyelinating event was 12 years (IQR 8–20 years). Patients were taking etanercept (34%), infliximab (29%), adalimumab (29%), or certolizumab (8%) at study entry. At least 1 additional comorbidity was reported in 62% of patients with recorded incident demyelination. Cardiovascular events (20%), asthma (17%), and depression (17%) were the most common comorbidities reported overall. In males, asthma (20%), liver disease (20%), and depression (20%) were most commonly reported; cardiovascular disease (24%), asthma (16%), and depression (16%) were the most common in females (table e-2, links.lww.com/NXI/A467).

Demyelinating events occurred a median of 3 years (IQR 1–5, range 0.2–12.1 years) from anti-TNF α initiation. Of the individuals who had demyelinating events, 13 (37%) occurred within 2 years and 24 (69%) within 5 years. Twenty-six of 35 events (74%) were reported in individuals taking anti-TNF α therapy at the time of event report. Of the 9 events that occurred in individuals not on therapy, 6 (67%) occurred within 90 days of stopping therapy, and 3 of 35 events (9%) had no recent exposure to anti-TNF α therapy. Nelson-Aalen cumulative hazard estimate plots indicated a steady event rate both in those with events occurring on treatment and those who had stopped treatment before event report (table 2 and figure).

The crude rate of incident demyelinating events was 19.7 per 100,000 person-years (95% CI 13.7–27.3). The crude rate in males was 22.1 per 100,000 (95% CI 10.6–40.7) and in females 18.8 per 100,000 (95% CI 12.2–27.8).

The SIR (age and sex corrected with Ref. 11 as the reference population) was 1.38 (95% CI 0.96–1.92) compared with the UK Hospital Episode Statistics/General Practice Research Datalink population (total population 24,052,635)¹¹ (table 3). The SIR was not significantly increased in females (SIR 1.15, 95% CI 0.74–1.69) but was raised in males (SIR 2.75, 95% CI 1.32–5.06) (table 3). Interaction testing was not performed on the SIR due to this being based on population structure.

Table 1 Characteristics of Patients With Incident Demyelinating Events

	Total	Male	Female
N	35	10	25
At register entry			
Age, median (IQR)	44 (37–57)	45 (34–53)	44 (39–60)
Sex, n (%) female	25 (71%)	—	—
Disease duration, median (IQR)	8 (4–16)	5 (1–8)	9 (6–21)
Tender joint count, median (IQR)	8 (3–16)	8 (2–17)	8 (3–14)
Swollen joint count, median (IQR)	7 (3–13)	4 (2–11)	9 (5–14)
ESR, median (IQR)	26 (17–79)	25 (19–87)	28 (16–74)
CRP, median (IQR)	32 (11–99)	32 (6–148)	38 (16–79)
DAS28 score, median (IQR)	5.9 (5.3–6.8)	6.0 (4.1–6.8)	5.9 (5.5–6.9)
Indication, n (%)			
Rheumatoid arthritis, RA	25 (71%)	6 (60%)	19 (76%)
Ankylosing spondylitis, AS	5 (14%)	2 (20%)	3 (12%)
Psoriatic arthritis, PSA	2 (5%)	1 (10%)	1 (4%)
Other	3 (9%)	1 (10%)	2 (8%)
Baseline steroids, n (%) yes	18 (51%)	6 (60%)	12 (48%)
Biologic at registration, n (%)			
Etanercept	12 (34%)	4 (40%)	8 (32%)
Infliximab	10 (29%)	1 (10%)	9 (36%)
Adalimumab	10 (29%)	3 (30%)	7 (28%)
Certolizumab	3 (8%)	2 (20%)	1 (4%)
Comorbidities, n (%)			
0	14 (38%)	3 (30%)	11 (44%)
1	9 (23%)	4 (40%)	5 (20%)
2	10 (33%)	4 (40%)	7 (28%)
3+	2 (6%)	0	2 (8%)
Smoking status, n (%)			
Current smoker	7 (21%)	4 (40%)	3 (13%)
Former smoker	13 (38%)	2 (20%)	11 (45%)
Never smoked	14 (41%)	4 (40%)	10 (42%)
At time of event			
Age, median (IQR)	50 (43–59)	48 (35–59)	50 (45–60)
Disease duration, median (IQR)	12 (8–20)	9 (4–11)	15 (10–24)
DAS28 score, median (IQR)	4.1 (2.8–5.0)	4.2 (2.5–4.9)	3.4 (3.0–5.1)
Biologic at event, n (%)			
Etanercept	6 (17%)	2 (20%)	4 (16%)
Infliximab	1 (3%)	0	1 (4%)
Adalimumab	11 (31%)	4 (40%)	7 (28%)

Continued

Table 1 Characteristics of Patients With Incident Demyelinating Events (*continued*)

	Total	Male	Female
Certolizumab	3 (8%)	1 (10%)	2 (8%)
Rituximab	4 (12%)	1 (10%)	3 (12%)
Anakinra	1 (3%)	0	1 (4%)
Off biologic	9 (26%)	2 (40%)	7 (28%)
Years from the start of the first anti-TNF to event			
Median (IQR)	3 (1–5)	3 (2–5)	3 (1–5)
Range (min, max)	0.2, 12.1	1.3, 9.0	0.2, 12.1
Occurred within 2 y, n (%)	13 (37%)	4 (40%)	9 (36%)
Occurred within 5 y, n (%)	24 (69%)	6 (60%)	18 (72%)

Abbreviations: IQR = interquartile range; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

Sensitivity analyses provided a similar estimate, excluding those with possible demyelination and including only those with definite/probable demyelination gave an overall SIR of 0.83 (95% CI 0.51–1.26); 0.69 (95% CI 0.39–1.14) in females and 1.65 (95% CI 0.61–3.59) in males (table e-3a, links.lww.com/NXI/A467). Restricting the population to only those with RA (i.e., excluding those with other rheumatologic diagnoses) gave similar results—the overall SIR was 1.10 (95% CI 0.71–1.63); sex-disaggregated rates were 0.95 (95% CI 0.57–1.49) in females and 2.21 (0.81–4.80) in males (table e-3b, links.lww.com/NXI/A467). Because of the small numbers of patients with diagnoses other than RA (ankylosing spondylitis: n = 5 and psoriatic arthritis: n = 2), it was not appropriate to calculate the SIR for demyelination in either of these diagnoses.

Across the cohort, there was a variable amount of clinical data available. From the data available, 11 cases were judged to have an initial presentation of possible or definite MS; however, in those with insufficient data available to positively diagnose MS, this could not be excluded. There were insufficient data available for the majority of cases to identify MS

subtype. Cases that did not meet the criteria for MS would all meet the criteria for clinically isolated syndrome. No cases had data available suggesting a diagnosis of neuromyelitis optica spectrum disorder, but cases could have been missed due to insufficient data. There were 12 reported cases of optic neuritis, some of whom met the diagnostic criteria for MS. Similarly, 10 reports indicated transverse myelitis, again some as presenting symptom of MS. A number of cases had MRI reports available, but not all cases, and although MRI findings were taken into account when reviewing the data, given the inconsistency in data availability, the findings are not reported. Data regarding treatment for demyelinating events were not routinely available and so were not analyzed.

Discussion

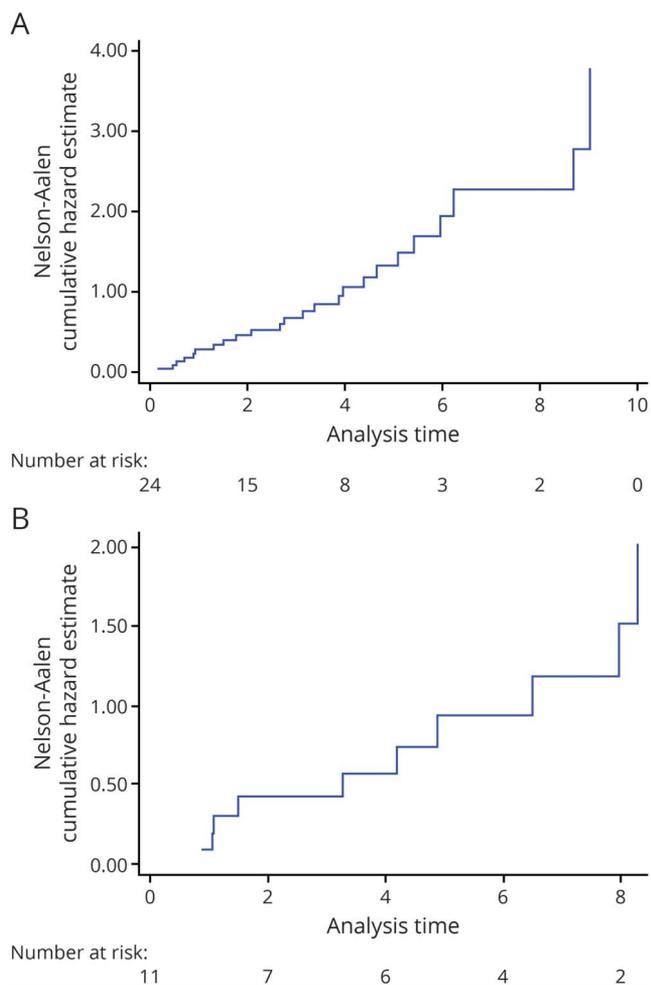
Our data support there being no substantial effect on the risk of incident demyelination associated with anti-TNF α therapy in a large, registry-based cohort. Although the SIR is marginally increased when looking at all incident demyelinating events, the CI crosses one, and this small effect is lost in both

Table 2 Time to Event From the Start of Anti-Tumor Necrosis Factor Alpha Therapy According to Event Occurring on or off Biologic Agent

	Demyelinating events occurring on biologic agent (n = 26)	Demyelinating events occurring off biologic agent (n = 9)
Time from drug start to event (median, IQR, range)	3.2 y (IQR 1.3–5.4; range 0.2–12 y)	3.3 y (IQR 1.1–4.9; range 0.9–8 y)
Occurred within 2 y, n (%)	9 (35%)	4 (44%)
Occurred within 5 y, n (%)	18 (69%)	6 (67%)
Median time since last biologic (median, IQR, range)	—	3 mo (IQR 2–11; range 1–48 mo)
Occurred within 90 d of therapy cessation, n (%)	—	6 (67%)

Abbreviation: IQR = interquartile range.

Figure Nelson-Aalen Cumulative Hazard Estimate Plots



(A) Nelson-Aalen cumulative hazard estimate plot showing time to event from start of drug in patients still on biologics. (B) Nelson-Aalen cumulative hazard estimate plot showing time to event from start of drug in patients off biologics.

of the sensitivity analyses. Furthermore, the crude incidence is similar when disaggregated by sex. This finding of a lack of a marked effect is in keeping with recent data originating from Scandinavian registries.¹² This result is in contrast to a recent case-control study from the United States¹³; however, differences in study design and statistical analysis prevent direct comparison. The BIOGEAS registry study reported a lower crude incidence (0.33 cases per 1,000 patients) than reported here¹⁴; however, the significant heterogeneity between studies prevents direct comparison. Of note, the BIOGEAS report does not list the cohort characteristics of included patients, further limiting comparison.

We are able to significantly extend previously published work by providing a rigorous review of included cases, with time-based survival analysis and a clear demographic and disease-specific picture of those with CNS demyelinating events. Particular strengths of this study include the registry-type design with prospective acquisition of both treatment and

events, along with the clinical data that is captured on each individual. Demyelination is an adverse event of interest in the BSRBR-RA, meaning that clinicians are alerted to report such events—as such most events in those reporting follow-up data are likely to have been captured.

It must be noted that we could not undertake a comparative analysis with patients with similar disease characteristics receiving conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; such as methotrexate and sulfasalazine) on this occasion. The BSRBR-RA does follow a relatively small cohort ($n = 3,700$) of patients receiving csDMARDs, but this cohort is limited to patients with RA. At the time of data extraction for our study, there were no reports of new/incident demyelinating disease in the group receiving csDMARDs.

With a median age of 44 years at BSRBR-RA entry and 50 years at the time of event, this population has an older age at incident demyelinating event than the UK MS population, who have a median age at onset of 37 years.¹¹ The crude incidence rate of 19.7/100,000 patient-years appears to be potentially double that seen in the background UK population ($c10/100,000$ pt years)¹⁵; however, given differences in population structure, these raw rates should not be directly compared.

Of interest, the crude rate reported in our study is about 50% of that reported in Scandinavian registries.¹² It must be noted that both the case definition and rigorous review of included cases prevent direct comparison between the 2, as we excluded peripheral demyelinating events, as their underlying etiology and causation pathways are thought to be different.¹⁶ The Scandinavian study including all central and peripheral demyelinating events recorded in medical registries, and thus, they would be expected to report a higher event incidence. CNS demyelinating events appear to occur at a consistent rate within our population, and there does not appear to be a marked change with cessation of therapy. However, it must be noted that there were only 3 events occurring >3 months following therapy cessation, which limits the conclusions that can be drawn from this.

The increased SIR that appears to be present in males is of interest. Conclusions regarding this are limited due to the small sample size and the fact that the CIs around the crude rates substantially overlap. However, a similar signal of increased risk in males is seen in the Danish cohort, but not the Swedish.¹² This sex-specific signal is lost in both of the sensitivity analyses. Of interest, in this cohort, males were more likely to smoke than females; smoking is associated with an OR of MS of 1.54,¹⁷ and so one potential hypothesis is that nonpharmacologic factors may be contributing to this observation.

A potential confounder is the increased risk of MS in individuals with autoimmune disease. However, a previous meta-

Table 3 SIR Compared With English Population Data (General Practice Research Datalink and Hospital Episode Statistics) From 1997 to 2010¹¹

	Biologic cohort		
	Observed	Expected	SIR (95% CI)
Female	25	21.78	1.15 (0.74–1.69)
Male	10	3.63	2.75 (1.32–5.06)
Total	35	25.41	1.38 (0.96–1.92)

Abbreviation: SIR = standardized incident rate.
"SIR" for demyelination events per 100,000 population.

analysis did not demonstrate an association between MS and RA (OR 1.15, 95% CI 0.77–1.73, $p = 0.49$), whereas a small but significant increase in the odds of comorbid psoriasis was seen in MS (OR 1.31, 95% CI 1.09–1.57, $p < 0.0001$).¹⁸ However, this small effect size would not be sufficient to show a signal in our cohort, particularly given the low number of individuals with psoriatic arthritis. It is more likely that where an increased SIR is seen, this is related to the fact that demyelination is an adverse event of interest in the BSRBR-RA, compared with population-based registries using GP data, and that this cohort of patients have increased health care contacts compared with the overall UK population at risk of MS.

This study is not without limitations. The BSRBR-RA is a real-world registry study: it records events, but clinicians remain responsible for treatment decisions and patients are under routine medical care. Given the well-documented concerns regarding the use of anti-TNF α therapies in those at risk of demyelination, they are likely to have been avoided in the highest risk cohort, such as those with a significant family history. The study cohort cannot therefore be assumed to have the same baseline risk of demyelination as the background population. Clinically reported events often had incomplete data, meaning that events may have been incorrectly assigned as possible rather than probable or definite, and this may partially explain the difference in results compared with the study from the United States, which had greater access to complete patient records.¹³

We did not have access to the source medical notes for individuals in whom demyelination was reported, meaning that ancillary and/or follow-up investigations were often not available. It is likely that at least some of those with events reported off therapy had demyelinating events that precipitated therapy withdrawal; however, given the similar and steady rate of decay seen in both groups, this is unlikely to have impacted on the results or their interpretation. The range of clinical phenotypes reported in the clinical data available suggests that there is no typical demyelinating presentation; however, given the limited and variable amount of data available, conclusions regarding clinical phenotypes must be guarded.

In conclusion, therefore, we find no convincing evidence of a strong impact of anti-TNF α therapy on risk of incident demyelination. Where demyelinating events are seen, there was no particular predilection for any particular CNS location or patient group. In addition, the signal of a possible small increased risk compared with the general population is lost in both of the sensitivity analyses. The small number of events (35) seen in a case population of >13,000 may be reassuring to both patients and clinicians considering the use of these therapies. However, given the serious nature of this potential outcome, careful consideration should still be given to their use and monitoring, particularly in those individuals at highest risk of demyelinating events.

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Disclosure

T.R.P. Taylor has no relevant conflicts to declare. J. Galloway has received speaker honoraria from AbbVie, BMS, Celgene,

Chugai, Gilead, Janssen, Lilly, Pfizer, Novartis, and UCB. R Davies has no relevant conflicts to declare. K. Hyrich reports nonpersonal grant income from Pfizer and BMS and nonpersonal honoraria from AbbVie. R. Dobson has no conflicts of interest with direct relevance to this work. She has received grant income from Biogen, Merck, and Celgene and honoraria/support for educational activities from Merck, Biogen, Teva, Roche, and Sanofi Genzyme. Go to Neurology.org/NN for full disclosures.

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Rebecca Davies, MSc	Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content, and analysis or interpretation of data
Kimme Hyrich, FRCP, PhD	Centre for Epidemiology Versus Arthritis, The University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom; National Institute of Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
Ruth Dobson, MRCP, PhD	Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, United Kingdom; Department of Neurology, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

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