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# Clinical Features and Genetic Risk of Demyelination Following Anti-TNF Treatment

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## Abstract

**Background:** Anti-TNF exposure has been linked to demyelination events. We sought to describe the clinical features of demyelination events following anti-TNF treatment and to test whether affected patients were genetically predisposed to multiple sclerosis [MS].

**Methods:** We conducted a case-control study to describe the clinical features of demyelination events following anti-TNF exposure. We compared genetic risk scores [GRS], calculated using carriage of 43 susceptibility loci for MS, in 48 cases with 1219 patients exposed to anti-TNF who did not develop demyelination.

**Results:** Overall, 39 [74%] cases were female. The median age [range] of patients at time of demyelination was 41.5 years [20.7–63.2]. The median duration of anti-TNF treatment was 21.3 months [0.5-99.4] and 19 [36%] patients were receiving concomitant immunomodulators. Most patients had central demyelination affecting the brain, spinal cord, or both. Complete recovery was reported in 12 [23%] patients after a median time of 6.8 months [0.1–28.7]. After 33.0 months of follow-up, partial recovery was observed in 29 [55%] patients, relapsing and remitting episodes

in nine [17%], progressive symptoms in three [6%]: two [4%] patients were diagnosed with MS. There was no significant difference between MS GRS scores in cases (mean -3.5 × $10^{-4}$, standard deviation [SD] 0.0039) and controls [mean -1.1 × $10^{-3}$, SD 0.0042] [$p = 0.23$].

**Conclusions:** Patients who experienced demyelination events following anti-TNF exposure were more likely female, less frequently treated with an immunomodulator, and had a similar genetic risk to anti-TNF exposed controls who did not experience demyelination events. Large prospective studies with pre-treatment neuroimaging are required to identify genetic susceptibility loci.

**Key Words:** Demyelination; anti-TNF

## 1. Introduction

Anti-TNF therapies were licensed for use in 1998 and have revolutionised the management of a range of immune-mediated inflammatory disorders. Case reports linking infliximab and etanercept to demyelination events followed and prompted the Food and Drug Administration and the European Medicines Agency to issue safety warnings.[1–3] Contemporaneously, a randomised controlled trial of lenercept [a recombinant TNF receptor p55 immunoglobulin fusion protein] in patients with multiple sclerosis was discontinued early, because of the increased frequency of early and more severe demyelination exacerbations in the treatment compared with placebo arms.[4]

Demyelinating events have been reported with all licensed anti-TNF therapies in the treatment of patients with inflammatory bowel disease[IBD],[5] rheumatoid arthritis,[6] and psoriasis.[7] Because demyelination was rare in the respective registration trials it is not possible to conclude whether a causal association exists between anti-TNF therapies and demyelination events.[7,8] Data from post-marketing adverse event registries seem to be reassuring, citing rates of demyelination similar to the background risk of multiple sclerosis.[9] However, these data are likely to underestimate rates of anti-TNF related demyelination because of confounding by voluntary reporting. In support of this assertion, data from a Danish population-based cohort study of patients with IBD treated with at least one anti-TNF reported a 2-fold relative risk of demyelinating events.[10] Moreover, because demyelination can be clinically silent, the actual risk attributable to anti-TNF therapies maybe even higher. Evidence of demyelination was reported in 4% of patients with rheumatoid arthritis or spondyloarthopathies treated with anti-TNF therapies after 18 months, in whom pre-treatment magnetic resonance imaging [MRI]was normal.[11]

Considerable uncertainty remains, therefore, as to whether anti-TNF exposure induces demyelination in patients genetically predisposed to multiple sclerosis, or is a chance observation reflecting the evolution of de novo multiple sclerosis, or is an idiosyncratic drug reaction. Moreover, because symptomatic demyelination events following anti-TNF are uncommon, their natural history is poorly defined.

## 2. Methods

### 2.1. Study design and setting

We conducted a retrospective case-control study to report the clinical features and natural history of demyelination events following anti-TNF therapy. We sought to assess whether demyelination events occurred in patients at increased genetic risk for multiple sclerosis.

### 2.2. Study populations

Potential cases were recruited from 41 UK and six international sites between 2012 and 2018. Patients were identified through opportunistic clinical encounters and through cases reported to the British Neurological Surveillance Unit [BNSU] or to the Medicine and Healthcare Products Regulatory Authority Yellow Card scheme.

Inclusion criteria were all of the following: exposure to anti-TNF drug[s] without a preceding history of neurological symptoms suggestive of demyelination; neurological symptoms persisting for at least 24 h following anti-TNF exposure; MRI brain and/or spinal cord imaging and/or or electrophysiological studies [nerve conduction or evoked potentials] consistent with central nervous system [CNS] or peripheral nervous system [PNS] disease, respectively; and neurological opinion implicating the anti-TNF drug as a cause of demyelination, necessitating drug withdrawal if the patient was still receiving the drug.

Investigators at each site completed a custom-designed case report form [Supplementary Appendix 1–3, available as Supplementary data at *ECCO-JCC* online], that captured the following data: patient demographics [age, weight, height, ethnicity, smoking, and inflammatory disease history]; drug exposure data [anti-TNF, anti-TNF dose, drug start date, drug stop date]; and demyelination history [onset, duration, resolution, investigations, and treatment].

Case report forms and supporting imaging and/or electrophysiological tests were reviewed independently by a panel including a neuroradiologist and at least two neurologists [Supplementary Appendix 1, available as Supplementary data at *ECCO-JCC* online]. Consistent with our previous pharmacogenetic studies,[12–14] we modified the Liverpool Adverse Drug Reaction Causality Assessment Tool to verify cases [Supplementary Figure 1, available as Supplementary data at *ECCO-JCC* online]. 'Possible' cases were defined as patients who had equivocal investigations or clinical features of demyelination. 'Probable' cases demonstrated clinical, radiological, and/or electrophysiological features of demyelination with a clear temporal relationship with anti-TNF therapy and no other cause for demyelination. In addition to these criteria, 'definite' cases were individuals who had a recurrence of demyelination on anti-TNF therapy re-challenge. Cases assigned as 'unlikely' were excluded. Definite, probable, and possible cases were included in subsequent analyses. We classified patients according to whether they had central [brain and/or spinal cord] or peripheral nervous system involvement and whether their illness was a clinically isolated syndrome or had a relapsing phenotype. A clinically isolated syndrome was defined as a first episode of neurological symptoms lasting for 24 h and is caused by inflammation or demyelination in the central nervous system. Partial recovery was defined as an episode of demyelination with partial or no resolution of symptoms at the time of follow-up.

Patients recruited to the Personalising Anti-TNF Therapy in Crohn's disease [PANTS] study without a history of demyelination were used as controls. In brief, the PANTS study is a UK-wide, multicentre, prospective observational cohort study of 1610 patients with Crohn's disease treated with infliximab (originator, Remicade [Merck Sharp & Dohme, UK] and biosimilar, CT-P13 [Celltrion, South Korea]),

and adalimumab (Humira [Abbvie, USA]).[15] To allow us to identify phenotypic factors associated with demyelination following anti-TNF therapy, each IBD case was matched to five anti-TNF exposed controls from the PANTS cohort by duration of anti-TNF therapy. Genetic risk scores for multiple sclerosis in all cases were compared with scores from control patients without neurological adverse events included in the genetics arm of the PANTS study.

### 2.3. Genetic methods

DNA was extracted from whole blood and genotyped using the Infinium Global Screening [cases] and Illumina CoreExome microarrays [controls]. Individuals of non-European ancestry were identified using principal component analyses and excluded. Checks were made for relatedness using KING 1.9. [16]

Variants with a genotype call rate of <95%, with a minor allele frequency of less than 1%, or with significant evidence of deviation from Hardy-Weinberg equilibrium [$p < 1 \times 10^{-6}$] were excluded. We corrected for batch-effect by removing variants with an uncorrected $p$-value of <0.05 for association with batch using Fisher's exact test. Palindromic variants were also removed before imputation, leaving 130 132 genotyped variants. Single nucleotide polymorphisms were imputed using the Sanger Imputation Service to the Haplotype Reference Consortium [HRC] panel, and a post-imputation information score [INFO score] of 0.9 was used as a cut-off. We constructed a multiple sclerosis genetic risk score [GRS] using data from previously identified risk variants.[17] Genetic risk scores were generated by summing the carriage status at each locus multiplied by the log odds ratio of that variant.[18,19] Susceptibility loci included in our GRS were defined as risk variants with a $p$-value $< 5 \times 10^{-6}$ and no closer in the genome than within 1 mega-base of another risk variant with a lower $p$-value. Overall, 51 loci were identified; details of their odds ratios and relative weightings are given in Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online.

We validated our GRS using subjects with multiple sclerosis identified in the UK Biobank, a study of over 500 000 individuals aged between 37 and 73 years recruited between 2006 and 2010. [20] Multiple sclerosis cases were defined in the UK Biobank using either the International Classification of Diseases [ICD] 10 code G35, ICD9 code 340, or self-report code 1261. Those with other demyelinating conditions, defined by an ICD10 code of G36/G37, ICD9 code of 341, or self-report code of 1397, were excluded. We validated the GRS in unrelated Europeans only. European ancestry was determined using principal components analysis and relatedness was determined using KING Kinship.[16] Imputation was performed by the UK Biobank.[21] The dataset used for validation of the GRS contains 1680 multiple sclerosis cases and 387 932 controls.

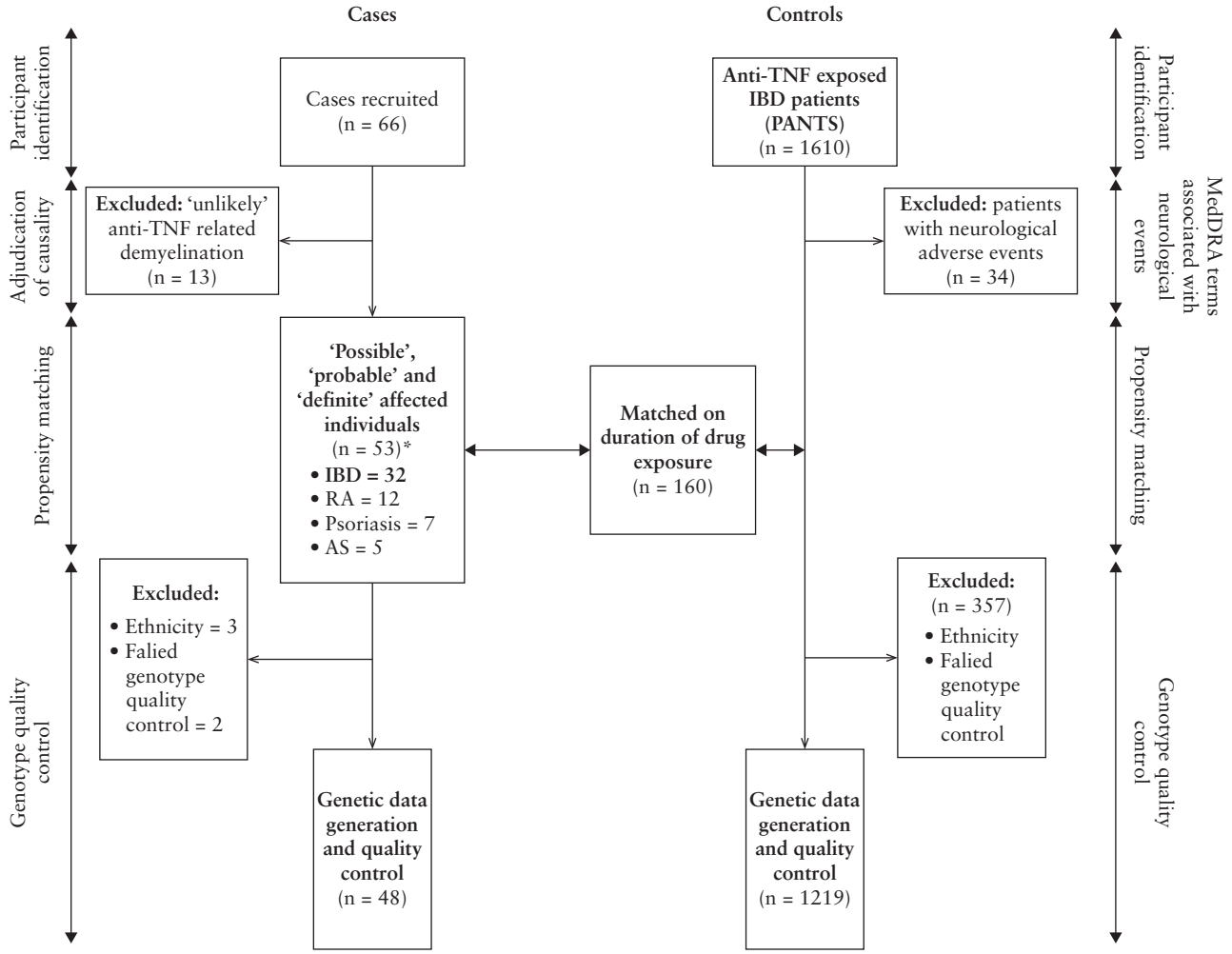


**Figure 1.** Flow diagram and study overview of case and control cohorts. *Three patients received anti-TNF therapy for more than one indication. IBD, inflammatory bowel disease; PANTS, Personalised Anti-TNF Therapy in Crohn's disease; MedDRA, Medical Dictionary for Regulatory Activities; RA, rheumatoid arthritis; AS, ankylosing spondylitis; TNF, tumour necrosis factor.

**Table 1.** Baseline demographic of cases with demyelination related to anti-tumour necrosis factor [TNF] therapy.

| Characteristic | Cases |
|---|---|
| Patients, *n* | 53 |
| Gender | |
| Female | 39 [74%] |
| Male | 14 [26%] |
| Age [years] | |
| Mean [SD] | 40.6 [10.5] |
| Median [min., max.] | 41.5 [20.7, 63.2] |
| Ethnicity | |
| White European | 44 [83%] |
| Other White background | 4 [8%] |
| Mixed White and Asian | 2 [4%] |
| Any other Asian | 2 [4%] |
| Caribbean | 1 [2%] |
| BMI | |
| Median [min., max.] | 24.9 [18.0, 43.2] |
| Missing | 5 [9%] |
| Condition | |
| IBD | 32 [60%] |
| RA | 12 [23%] |
| Psoriasis | 7 [13%] |
| AS | 5 [9%] |
| Drug | |
| Infliximab | 25 [47%] |
| Adalimumab | 19 [36%] |
| Etanercept | 7 [13%] |
| Certolizumab | 1 [2%] |
| Golimumab | 1 [2%] |
| Family history | |
| Yes | 5 [9%] |
| No | 42 [79%] |
| Smoking | |
| Current | 13 [25%] |
| Ex | 13 [25%] |
| Never | 21 [40%] |
| Immunomodulator | |
| Yes | 19 [36%] |
| No | 34 [64%] |
| Duration on anti-TNF [months] | |
| Median [min., max.] | 21.3 [0.460, 99.4] |

BMI, body mass index; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; AS, ankylosing spondylitis; SD, standard deviation; min,. minimum; max, maximum.

### 2.4. Statistical methods

Pseudonymised data were managed using purpose-designed electronic data capture tools at the Royal Devon and Exeter NHS Trust. Statistical analyses were undertaken in R 3.6.1 [R Foundation for Statistical Computing, Vienna, Austria], PLINK version 1.90b3.42, and MATLAB version R2017a. All analyses were two-tailed and *p*-values <0.05 were considered significant.

Descriptive statistics were reported, based on normality, as mean (standard error of the mean [SEM]) and median [IQR] for continuous data and as proportions for categorical data unless otherwise stated. We included patients with missing clinical data in analyses for which they had data, and specified the denominator for each variable. Propensity matching of IBD cases to PANTS controls on duration of anti-TNF drug exposure was undertaken using the MatchIt package in R. [22]We performed univariable analyses, using Fisher's exact test for categorical data and Mann-Whitney U tests for continuous data, to identify clinical variables associated with demyelination events in cases versus controls.

**Table 2.** Characteristics of anti-TNF exposed inflammatory bowel disease cases and controls.

| Characteristic [IBD patients] | Cases *n* = 32 | Controls *n* = 160 | *p*-value |
|---|---|---|---|
| Sex | | | |
| Female | 27 [85%] | 92 [58%] | 0.008 |
| Male | 5 [16%] | 68 [43%] | |
| Age (median [IQR]) | 34.1 [29.546.5] | 33.9 [25.048.0] | 0.542 |
| BMI (median [IQR]) | 23.6 [20.627.1] | 24.1 [20.328.9] | 0.539 |
| Smoking | | | |
| Current | 6 [22%] | 27 [17%] | 0.75 |
| Ex | 9 [33%] | 50 [32%] | |
| Never | 12 [44%] | 81 [51%] | |
| Concurrent immunomodulator | 10 [31%] | 89 [56%] | 0.02 |

BMI, body mass index; TNF, tumour necrosis factor; IQR, interquartile range; IBD, inflammatory bowel disease.

We tested for differences in multiple sclerosis genetic risk scores between cases and controls both in the UK Biobank and in our case-control study of patients exposed to anti-TNF, using Student's t tests. Diagnostic performance of these scores was assessed using receiver operating characteristics [ROC] analyses. Fisher's exact test with Bonferroni correction was used to test association at each locus.

### 2.5. Ethical considerations

The protocol was approved by the National Research Ethics Committee [11/SW/0222, Exeter pharmacogenetic PRED4 programme], and international sites sought local ethical approval respectively. All participants involved provided informed written consent. Development and validation of the GRS was conducted using data from the UK Biobank [application 41588].

## 3. Results

### 3.1. Study overview

Case disposition through the study is shown in Figure 1. Between 2012 and 2018, 66 patients were recruited from 41 UK and six international sites. Following adjudication, we excluded 13 [20%] patients: seven [11%] in whom review of investigations refuted evidence of demyelination or of a temporal relationship with anti-TNF exposure; and six [9%] in whom an alternative diagnosis was more likely [mycoplasma infection, hypertension, vitamin B12 deficiency, mononeuritis multiplex, multifocal acquired demyelinating sensory and motor neuropathy, and myositis]. Only one patient was re-challenged with an anti-TNF drug after a demyelination event.

Control subject disposition through the study is shown in Figure 1. Overall, 2% [34/1610] patients suffered a neurological adverse event during follow-up in the PANTS study and were excluded from this control cohort. The adverse event was attributed to the anti-TNF drug in 24/34 patients, leading to drug withdrawal in half; however, following neurological assessment, none were diagnosed with demyelination.

After assessment using genetic quality control methods, we excluded five cases: three [6%] for non-White European ethnicity and two [4%] for failure of genotyping. We did not identify relatives of third degree or closer.

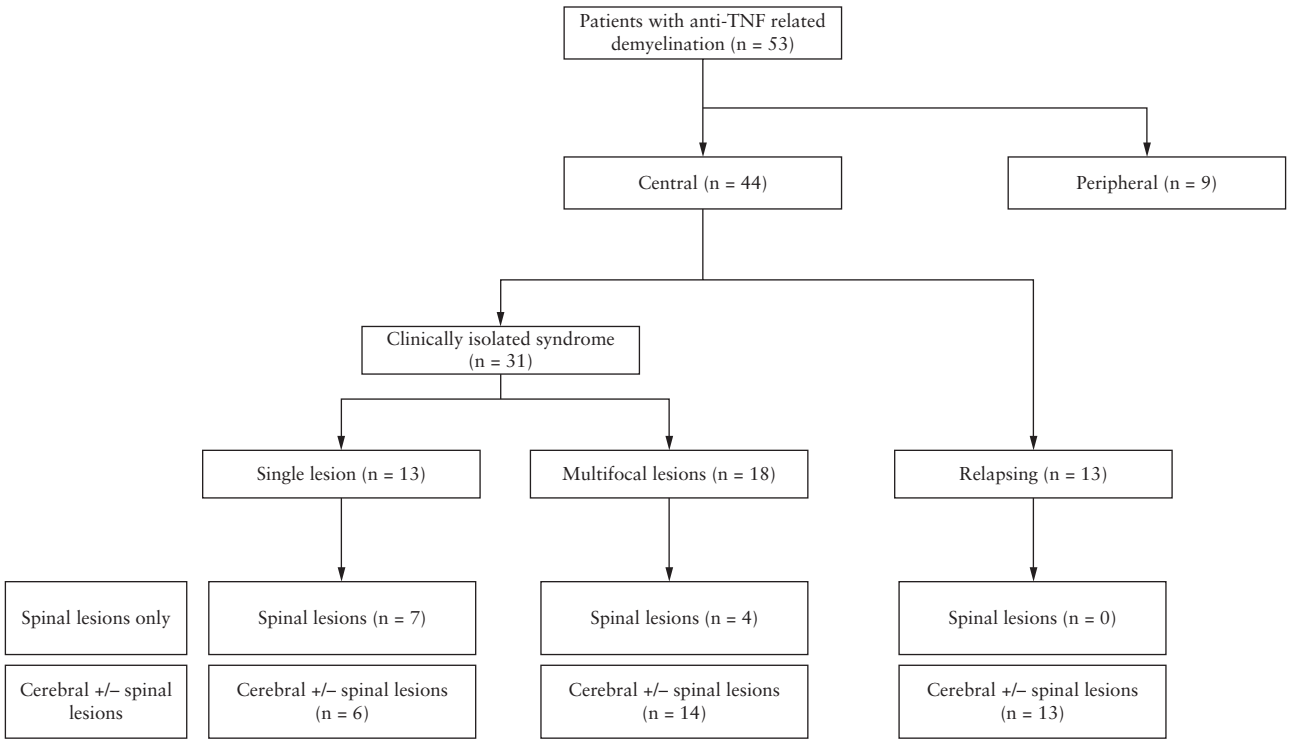


**Figure 2.** Pattern of anti-tumour necrosis factor [TNF] related demyelination in 53 cases.

**Table 3.** Clinical characteristics of demyelination events in anti-TNF exposed cases.

| Characteristic of demyelination events | Cases [*n* = 53] |
|---|---|
| Investigations | |
| Lumbar puncture | 32 [60%] |
| Nerve conduction studies | 8 [15%] |
| Electrophysiology | 19 [36%] |
| Treatment | |
| Steroids | 21 [40%] |
| IVIG | 8 [15%] |
| Plasma exchange | 4 [8%] |
| None | 24 [45%] |
| Other | 1 [2%] |
| Time to recovery [months] | |
| Median [min., max.] | 6.75 [0.10, 28.7] |
| Duration of follow-up [months] | |
| Median [min., max.] | 31.0 [2.00, 171] |

TNF, tumour necrosis factor; IVIG, intravenous immunoglobulin; min.,. minimum; max., maximum.

## 3.2. Clinical characteristics

The clinical features of verified cases are summarised in Table 1. Overall, 39 [74%] patients were female and 44 [83%] patients were White European. The median age [range] was 41.5 years [20.7–63.2]. Thirteen [25%] were current and 13 [25%] were ex-smokers. The indication for anti-TNF therapy was IBD in 32 [60%], rheumatoid arthritis in 12 [23%], psoriasis or psoriatic arthropathy in seven [13%], and ankylosing spondylitis in five [9%] patients, respectively. Three patients received anti-TNF therapy for more than one indication. Demyelination events followed treatment with infliximab in 25 [47%], adalimumab in 19 [36%], etanercept in seven [13%], golimumab in one [2%], and certolizumab in one [2%] patient[s]. Concomitant immunomodulator use was observed in 19 [36%] cases, (thiopurine in eight [42%], methotrexate in eight [42%], ciclosporin in two [11%], leflunomide in one [5%]). Overall, the median [range] duration of anti-TNF treatment before demyelination event was 21.3 [0.5–99.4] months.

Propensity matching in the subset of patients with IBD resulted in a median [IQR] duration of anti-TNF treatment before demyelination event of 9.9 [5.1-31.9] and 9.9 [5.1-25.2] months in cases and controls, respectively [$p$ = 0.44]. Cases were more likely to be female (84% [27/32] vs 58% [92/160], respectively, $p$ = 0.008, Table 2]) and were less likely to have been treated with a concomitant immunomodulator (immunomodulator 31% [10/32] vs 56% [89/160], respectively, $p$ = 0.02). No differences were seen according to age, ethnicity, body mass index [BMI], or cigarette smoking.

## 3.3. Natural history of demyelination

Five [9%] patients had a family history of multiple sclerosis, although none was a first-degree relative of a patient with multiple sclerosis. Four [8%] patients had a MRI of the brain or spinal cord before the index demyelinating event. Three MRI scans were conducted before drug commencement and between 12.0 and 108.0 months before the demyelinating event. The indications were paraesthesia, seizures, and those of an independent research study. Excluding the research MRI scan, none showed evidence of demyelination. The most common presentation was of central demyelination, observed in 44/53 [83%] patients; 31/44 [70%] patients with central demyelination had features in keeping with a clinically isolated syndrome [CIS]. Of these 13/31 [42%] patients were noted to have a single lesion on MRI, and the remaining 18 [58%] had multifocal lesions. Both cerebral and spinal lesions were noted [Figure 2].

The anti-TNF drug was withdrawn in all patients. In 24 [45%] patients no additional treatment was used; 21 [40%] patients received corticosteroids; eight [15%] were treated with intravenous immunoglobulin;

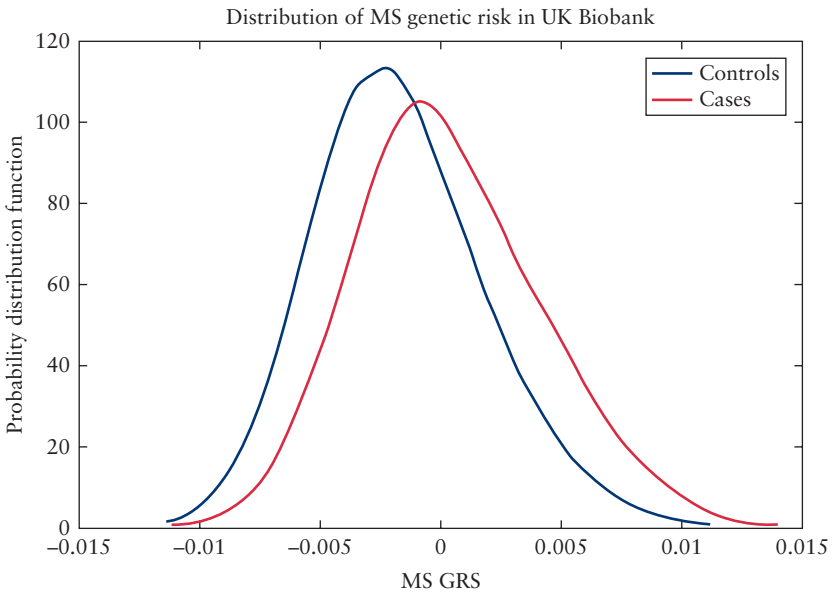


**Figure 3.** Probability distribution of genetic risk scores [GRS] in patients with multiple sclerosis [MS] in the UK Biobank.

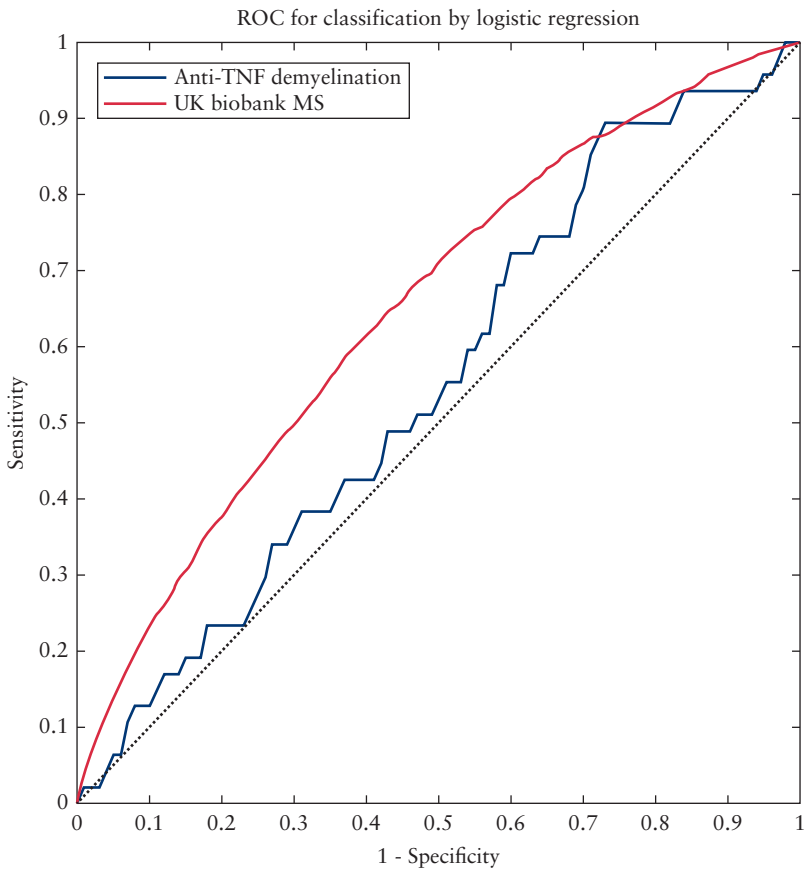


**Figure 4.** Receiver operating characteristic [ROC] curves of multiple sclerosis [MS] genetic risk scores [GRS] in MS patients in the UK Biobank and anti-TNF [tumour necrosis factor] related demyelination cases.

and four [8%] patients received plasma exchange [Table 3]. One patient, who was re-treated with an anti-TNF, developed symptoms of demyelination after each of two re-challenges. The median [range] duration of follow-up after the index demyelination event was 31.0 months [2.0–171.0]; only 5/53 [9%] patients had less than 6 months of follow-up. Complete recovery was reported in 12 [23%] patients after a median [range] time of 6.8 months [0.1–28.7], and partial recovery in 29 [55%] patients after a median [range] time of 33.0 months [2.0–118.0]

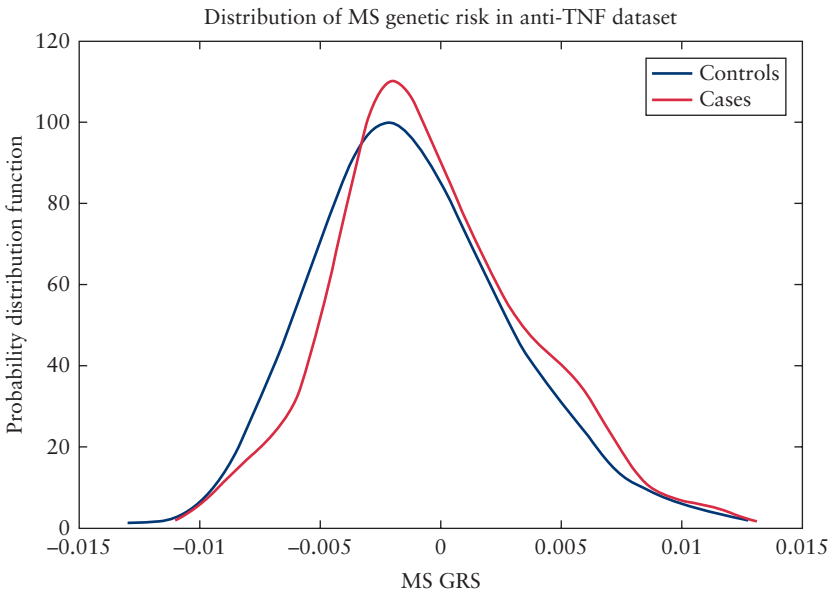


**Figure 5.** Probability distribution of genetic risk scores [GRS] in cases and controls. MS, multiple sclerosis.

of follow up. Relapsing and remitting episodes were observed in nine [17%] patients, and three [6%] patients experienced progressive symptoms; all patients with relapsing and remitting episodes or progressive symptoms had central demyelination. Overall, two [4%] patients were subsequently diagnosed with multiple sclerosis.

### 3.4. Genetic analysis

After genetic imputation, we excluded eight of the 51 target loci from the genetic risk score analyses: six loci because of poor imputation [INFO score <0.9] and two loci because they were not included in the HRC reference panel. The 43 loci that were used to construct our multiple sclerosis GRS are shown in Supplementary Table 1. We used this multiple sclerosis GRS in the UK Biobank and observed a significant difference between multiple sclerosis cases and controls [$p = 3.2 \times 10^{-116}$] [Figure 3] with an area under the curve [AUC] [95% CI] of 0.65 [0.64–0.66] [Figure 4].

There was no significant difference in multiple sclerosis GRS scores between cases and controls (cases [mean $-3.5 \times 10^{-4}$, SD 0.0039] vs. controls [mean $-1.1 \times 10^{-3}$, SD 0.0042], $p = 0.23$) [Figure 5]. Moreover, no significant associations with demyelination were seen at any individual locus [Supplementary Table 2, available as Supplementary data at *ECCO-JCC* online]. We did not observe genomic inflation for the single nucleotide polymorphisms [SNPs] used in our GRS [Supplementary Figure 2, available as Supplementary data at *ECCO-JCC* online]. The AUC [95% CI] for predicting anti-TNF related demyelination in our cases compared with PANTS control subjects was 0.55 [0.46–0.64] [Figure 4].

## 4. Discussion

### 4.1. Key results

Anti-TNF exposed patients who suffered demyelination events were more likely to be female and less frequently treated with an immunomodulator. Patients who developed demyelination events had similar genetic risk scores for multiple sclerosis to those of control patients who did not develop demyelination events after anti-TNF therapy. Following almost 3 years of follow-up, about half of our demyelination cases had received one or more treatments for demyelination and three-quarters had ongoing neurological symptoms.

### 4.2. Interpretation

Shared genetic susceptibility between autoimmune and inflammatory conditions may account for the increased risk of multiple sclerosis reported in patients with rheumatoid arthritis and IBD.[23,24] Previous genetic studies of anti-TNF induced demyelination are limited to a negative candidate gene study of *TNFRSF1A* in patients with rheumatoid arthritis.[25] Here, we have shown that anti-TNF treated patients who developed demyelination events had overlapping genetic risk scores for multiple sclerosis with those of anti-TNF exposed controls who did not develop demyelination. It is unlikely, then, that anti-TNF therapies lead to demyelination only in individuals genetically predisposed to multiple sclerosis. In support of this assertion, only two cases in our study were subsequently diagnosed with multiple sclerosis.

There was a female predominance among patients with demyelination following treatment with anti-TNF therapies. We did not observe any other classical risk factors for multiple sclerosis, arguing against the hypothesis that these events represent the chance development of de novo multiple sclerosis. For example, compared with previously reported case series of patients with multiple sclerosis, our cases were older[26] and less likely to be cigarette smokers,[27] and no one reported a first-degree relative with multiple sclerosis.[28] In support of anti-TNF related demyelination being an adverse drug reaction, we observed rapid recurrence of neurological symptoms in the one individual who was re-challenged with an anti-TNF drug after a demyelination event.

### 4.3. Limitations and generalisability

Our study has several strengths including rigorous cross-disciplinary independent case verification, and for the first time we explored the value of a multiple sclerosis GRS in a study of anti-TNF related demyelination. We acknowledge, however, the following important limitations: first, in keeping with all case-control studies, our data are susceptible to recall bias, with greater recruitment of more severe

cases. Second, because this was a convenience sample, we were unable to report the incidence of demyelination events. However, in our prospectively collected control cohort of 1610 patients, 2% reported neurological symptoms during follow-up although none was confirmed as being due to demyelination. Third, our retrospective data collection from medical records is subject to missingness and interpretation bias. In particular, we have no data relating to other important environmental risk factors for multiple sclerosis, including vitamin D deficiency and previous Epstein-Barr virus infection. Fourth, our genetic analyses were limited to patients of White European ancestry, and only patients with Crohn's disease made up the control cohort, which limits the generalisability of our findings. Finally, despite the study being open for 6 years, we accept that our sample size was too small to permit a pharmacogenetic genome-wide association study to identify novel variants associated with demyelination following treatment with anti-TNF, and we were also underpowered to detect a difference between our cases and multiple sclerosis cases from the UK Biobank.

### 4.4. Conclusion

This large case-control study adds comprehensive clinical information to the existing reports of demyelinating events associated with anti-TNF therapy for inflammatory disorders. Demyelination events were no more common in patients at genetic risk for multiple sclerosis. Further pharmacogenetic studies with prospective neuroimaging are required to define the risk of demyelination following anti-TNF therapy and to identify genetic susceptibility loci.

## Funding

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## Conflict of Interest

SL has received meeting support fees from Pfizer and Ferring; NC is funded by a Crohn's and Colitis UK fellowship; GJW has consulted for AbbVie and received honoraria from Falk and AbbVie for unrelated topics and a fellowship from NIHR; GAH reports non-financial support from AbbVie, outside the submitted work, and that he is now an employee of AbbVie and owns stock in the company; RJM has received honoraria and advisory board fees from Biogen, Novartis, Roche, Teva, Merck, and Eisai for unrelated topics; MSS has received advisory board, research support, and consulting and speaker fees for Janssen, Pfizer, AbbVie, and Takeda for unrelated topics; PMI has received lecture fees from AbbVie, Warner Chilcott, Ferring, Falk Pharma, Takeda, MSD, Johnson and Johnson, Shire and Pfizer, financial support for research from MSD, Takeda and Pfizer, advisory fees from Abbvie, Warner Chilcott, Takeda, MSD, Vifor Pharma, Pharmacosmos, Topivert, Genentech, Hospira, and Samsung Bioepis; NAK has consulted for Falk and received honoraria from Falk, Allergan, Pharmacosmos, and Takeda for unrelated topics, and is a deputy editor of *Alimentary Pharmacology & Therapeutics*; AS is a consultant to Medtronic for unrelated topics; TH has received honoraria for lectures, advisory board consultancy fees, acted as a principle investigator and chief investigator on clinical trials sponsored by and received support to attend meetings from Biogen, Allergan, Merz, GW Pharmaceuticals, Eisai, Ipsen, Roche, and Novartis for unrelated topics; JRG received honoraria from Falk, Abbvie, and Shield therapeutics for unrelated topics; TA has received unrestricted research grants, advisory board fees, speaker honorariums, and support to attend international meetings from AbbVie, Merck, Janssen, Takeda, Ferring, Tillotts, Ferring, Pfizer, NAPP, Celltrion, and Hospira for unrelated topics; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years. HDG, PH, NMH, BH, JH, AJC, GCF, ES FC, EL, VA, ARW, JT, RNB, and MNW have no conflict of interest to declare in relation to the work described.

## Author Contributions

AS, TH, NAK, JRG, and TA participated in the conceptualisation and design of the work. SL, HDG, PH, NMH, NC, BH, GJW, GAH, JH, RM, AC, MSS, PMI, GCF, ES, FC, EL, VA, ARW, JT, RNB, MW, NAK, AS, TH, JRG, and TA were involved in the acquisition, analysis or interpretation of data. The data analysis was performed by SL and HDG. Drafting of the manuscript was conducted by SL, HDG, NAK, JRG, and TA. All the authors contributed to the critical review and final approval of the manuscript. TA obtained the funding for the study and is the guarantor of the article.

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## Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

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