Clinical features and genetic risk of demyelination following anti-TNF treatment

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Authorship

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted

Contributions

A.S, T.H, N.A.K, J.R.G and T.A participated in the conception and design of the work. S.L, H.D.G, P.H, N.M.H, N.C, B.H, G.J.W, G.A.H, J.H, R.M, A.C, M.S.S, P.M.I, G.C.F, J.F.C, E.L, A.R.W, J.T, R.N.B, M.W, N.A.K, A.S, T.H, J.R.G and T.A were involved in the acquisition, analysis or interpretation of data. The data analysis was performed by S.L and H.D.G. Drafting of the manuscript was conducted by S.L, H.D.G, N.A.K, J.R.G and T.A. All the authors contributed to the critical review and final approval of the manuscript. T.A obtained the funding for the study and is the guarantor of the article.

Abstract

Background and Aims

Anti-TNF exposure has been linked to demyelination events. We sought to describe the clinical features of demyelination events following anti-TNF treatment and 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 treatment. We compared genetic risk scores (GRS), calculated using carriage of 43 susceptibility loci for MS, in 48 cases to 1219 control patients exposed to an anti-TNF who did not develop demyelination events.

Results

Overall, 39 (73.6%) cases were female with a median age (range) at the time of demyelination of 41.5 years (20.7 – 63.2). The median duration of anti-TNF treatment was 21.3 (0.5-99.4) months and 19 (36%) patients were treated with concomitant immunomodulators. Most patients had central demyelination affecting the brain, spinal cord or both. Complete recovery was reported in 12 (22.6%) patients after a median time of 6.8 (0.1 – 28.7) months. After 31 months of follow-up partial recovery was observed in 29 (54.7%) patients, relapsing and remitting episodes in 9 (17.0%), progressive symptoms in 3 (5.7%): 2 (4%) patients were diagnosed with MS. There was no significant difference between MS GRS scores in cases (mean -3.5×10^{-4}, 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 had a similar genetic risk to anti-TNF exposed controls who did not. Pharmacogenetic studies with prospective neuroimaging are required to test whether demyelination events following anti-TNF are an idiopathic drug reaction.

Introduction

Anti-TNF therapies were licensed for use in 1998 and have revolutionised the management of 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].

Demyelination events have been reported with all licensed anti-TNF therapies in the treatment of patients with inflammatory bowel disease[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 similar rates of demyelination 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 two-fold relative risk of demyelination 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 after 18 months in whom pre-treatment MRI imaging was normal [11].

Considerable uncertainty remains, therefore, as to whether anti-TNF exposure induces demyelination in patients genetically pre-disposed to multiple sclerosis or is a chance observation reflecting the evolution of de novo multiple sclerosis, or an idiosyncratic drug reaction. Moreover,

because symptomatic demyelination events following anti-TNF are uncommon their natural history is poorly defined.

Methods

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.

Study populations

Potential cases were recruited from 41 UK and 6 international sites between 2012 and 2018. Patients were identified through: opportunistic clinical encounters, cases reported to the British Neurological Surveillance Unit (BNSU) or to the Medicine and Healthcare Products Regulatory Authority pharmacovigilance 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 hours 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 (Supplemental Appendix 3), 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 neuro-radiologist and at least 2 neurologists. Consistent with our prior pharmacogenetic studies[12–14] we modified the Liverpool Adverse Drug Reaction Causality Assessment Tool to verify cases (Supplemental Figure 1). “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 rechallenge. 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. Clinically isolated syndrome was defined as a first episode of neurological symptom lasting for 24 hours and is caused by inflammation or demyelination in the central nervous system.

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, multicenter, 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 to scores from control patients without neurological adverse events included in the genetics arm of the PANTS study.

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%, a minor allele frequency of less than 1% or with significant evidence of deviation from Hardy-Weinberg equilibrium ($P<1\times10^{-6}$) 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 prior to 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 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 $p < 5 \times 10^{-6}$ 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 Supplemental Table 1.

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 ICD10 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[21,22]. Imputation was performed by the UK

Biobank[23]. The dataset used for validation of the GRS contains 1680 multiple sclerosis cases and 387,932 controls.

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 (SEM) and median [IQR] for continuous data and as proportions for categorical data. 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[24]. 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.

We tested for differences in MS 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.

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].

Results

Study overview

Case disposition through the study is shown in Figure 1. Between 2012 and 2018, 66 patients were recruited from 41 UK and 6 international sites. Following adjudication, we excluded 13 (20%) patients: 7 (11%) in whom review of investigations refuted evidence of demyelination or a temporal relationship with anti-TNF exposure; and 6 (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, 2.1% (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 5 cases: 3 (6%) for non-white European ethnicity and 2 (4%) for failure of genotyping. We did not identify relatives of third degree or closer.

Clinical characteristics

The clinical features of verified cases are summarised in Table 1. Overall, 39 (73.6%) 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 (60.4%), RA in 12 (22.6%), psoriasis or psoriatic arthropathy in 7 (13.2%), and ankylosing spondylitis in 5 (9.4%) 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 7 (13%), golimumab in 1 (1.9%) and certolizumab in 1 (1.9%) patient(s), respectively. Concomitant immunomodulator use was observed in 19 (36%) cases, (thiopurine 8 (42%), methotrexate 8 (42%), ciclosporin 2 (10.5%), leflunomide 1 (5.3%). Overall, the median (range) duration of anti-TNF treatment prior to 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 prior to 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 (84.4% [27/32] vs 57.5% [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 55.6% [89/160] respectively, p = 0.02). No differences were seen according to age, ethnicity, BMI or cigarette smoking.

Natural history of demyelination

Five patients had a family history of multiple sclerosis, although none were first degree relatives of a patient with multiple sclerosis. Four (8%) patients had a MRI brain or spinal cord before the onset of demyelination and none showed evidence of demyelination. The most common presentation was of central demyelination, observed in 44/53 (83.0%) patients. 31/44 (70.5%) patients with central demyelination had features in keeping with a clinically isolated syndrome (CIS). Of these 13/31 (41.9%) patients were noted to have a single lesion on MRI, and the remaining 18 (58.0%) multifocal lesions. Both cerebral and spinal lesions were noted (Figure 2).

The anti-TNF drug was withdrawn in all patients. In 24 (45.3%) patients no additional treatment was used, 21 (39.6%) patients received corticosteroids, 8 (15.1%) were treated with intravenous immunoglobulin and 4 (7.5%) patient 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 (2 - 171) months.

Complete recovery was reported in 12 (22.6%) patients after a median (range) time of 6.8 (0.1 – 28.7) months. Partial recovery was observed in 29 (54.7%) patients, relapsing and remitting episodes in 9 (17.0%), and 3 (5.7%) patients experienced progressive symptoms. Overall, 2 (4%) patients were subsequently diagnosed with multiple sclerosis.

Genetic Analysis

After genetic imputation, we excluded 8 of the 51 target loci from the genetic risk score analyses: 6 loci because of poor imputation (INFO score <0.9) and 2 loci because they were not included in the HRC reference panel. The 43 loci that were used to construct our MS GRS are shown in Supplementary Table 1. We used this MS GRS in the UK Biobank and observed a significant difference between MS cases and controls ($p = 3.2 \times 10^{-116}$) (Figure 3) with an area under the curve (95% CI) of 0.65 (0.64 – 0.66) (Figure 4).

There was no significant difference in MS GRS scores between cases and controls (cases [mean -3.5×10^{-4}, SD 0.0039] vs. controls [mean -1.1×10^{-3}, SD 0.0042], p=0.23) (Figure 5). Moreover, no significant associations with demyelination were seen at any individual locus (Supplementary Table 2). We did not observe genomic inflation for the SNPs used in our GRS (Supplementary Figure 2). 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).

Discussion

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 control patients who did not develop demyelination events after anti-TNF therapy. Following almost three years of follow-up, about half of our demyelination cases had received one or more treatments for demyelination and a quarter had ongoing neurological symptoms.

Interpretation

Shared genetic susceptibility between autoimmune and inflammatory conditions may account for the increased risk of multiple sclerosis reported in patients with RA and IBD[25,26]. Previous genetic studies of anti-TNF induced demyelination are limited to a negative candidate gene study of *TNFRSF1A* in patients with RA[27]. Here, we have shown that anti-TNF treated patients who developed demyelination events had overlapping genetic risk scores for multiple sclerosis with anti-TNF exposed controls who did not develop demyelination. It is unlikely, then, that anti-TNF therapies lead to demyelination only in individuals genetically pre-disposed 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 amongst 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 to previously reported case series of patients with multiple sclerosis our cases were older [28], less likely to be cigarette smokers [29] and no one reported a first degree relative with multiple sclerosis [30] . 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.

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 an MS 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 were confirmed as being due to demyelination. Third, our retrospective data collection from medical records is subject to missingness and interpretation bias. 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 six years we accept that our sample size was too small to permit a pharmacogenetic genome wide association study to identify novel variants associated with anti-TNF related demyelination and we were also underpowered to detect a difference in our cases and MS cases from the UK Biobank.

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 test whether anti-TNF related demyelination is an idiopathic drug reaction.

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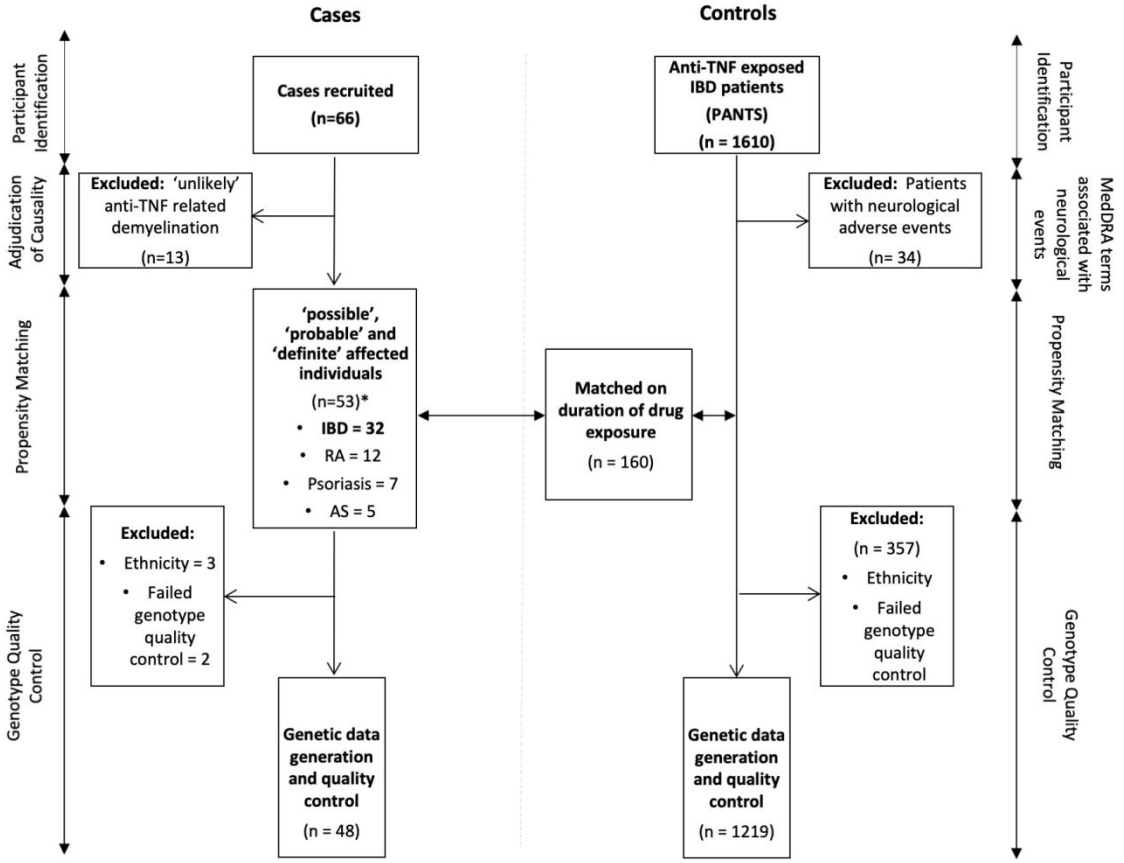
Figures and Tables

Figure 1. Flow diagram and Study Overview of Case and Control Cohorts



* Three patients received anti-TNF therapy for more than one indication

Abbreviations: 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

389 **Figure 2. Pattern of anti-TNF related demyelination in 53 cases**

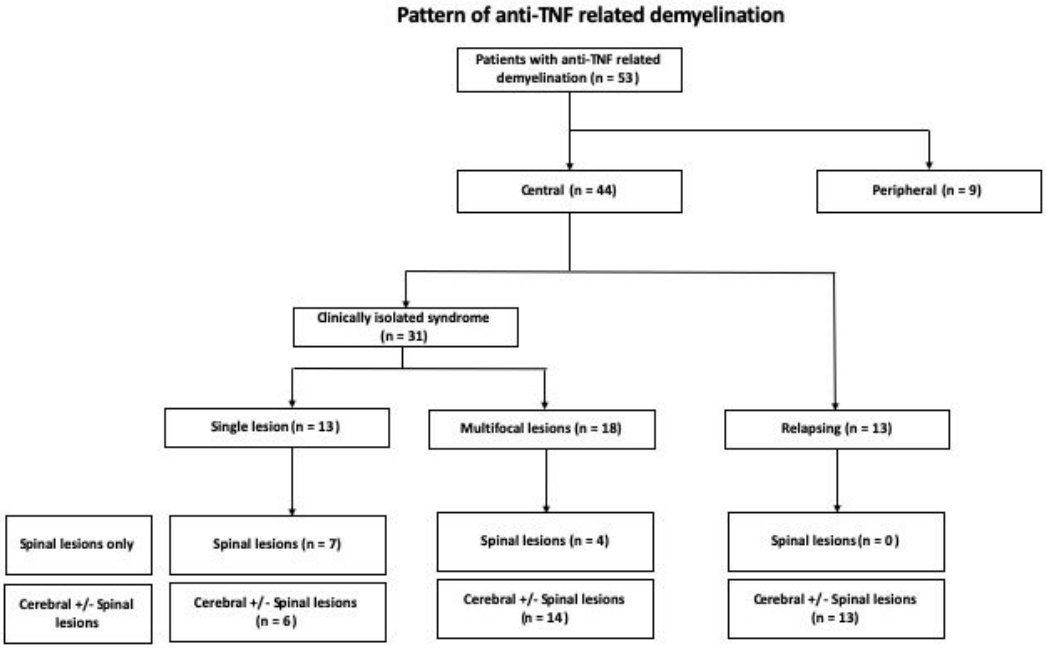


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Figure 3. Probability distribution of genetic risk scores (GRS) in patients with multiple sclerosis in the UK Biobank

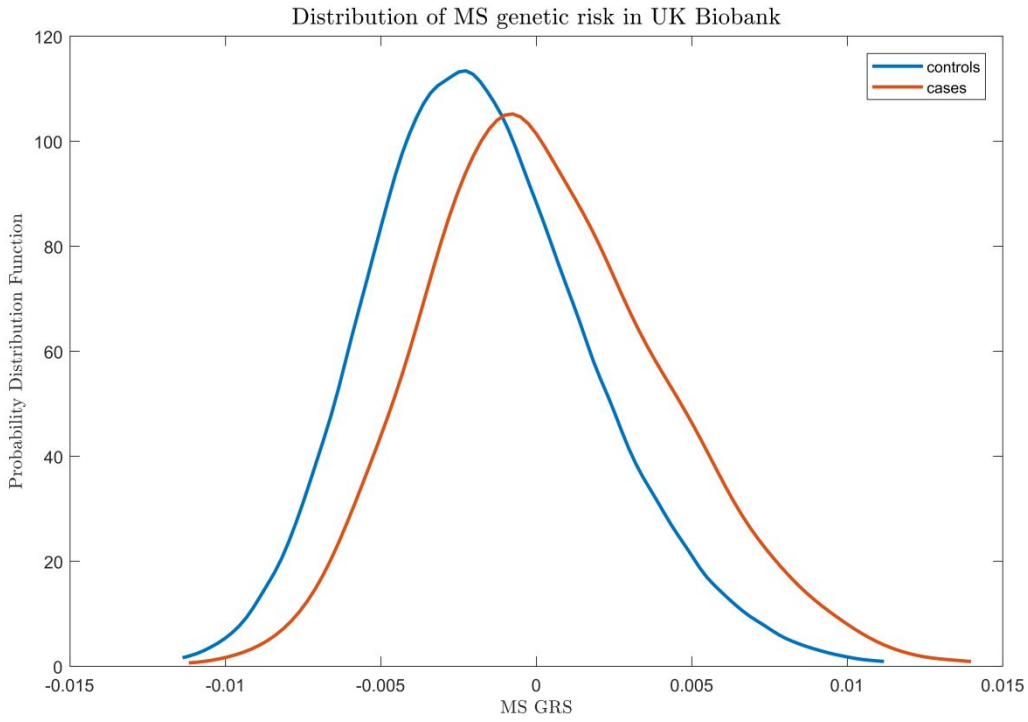

Figure 4. Receiver operating characteristic (ROC) curves of multiple sclerosis (MS) genetic risk scores (GRS) in MS patients in the UK Biobank and anti-TNF related demyelination cases

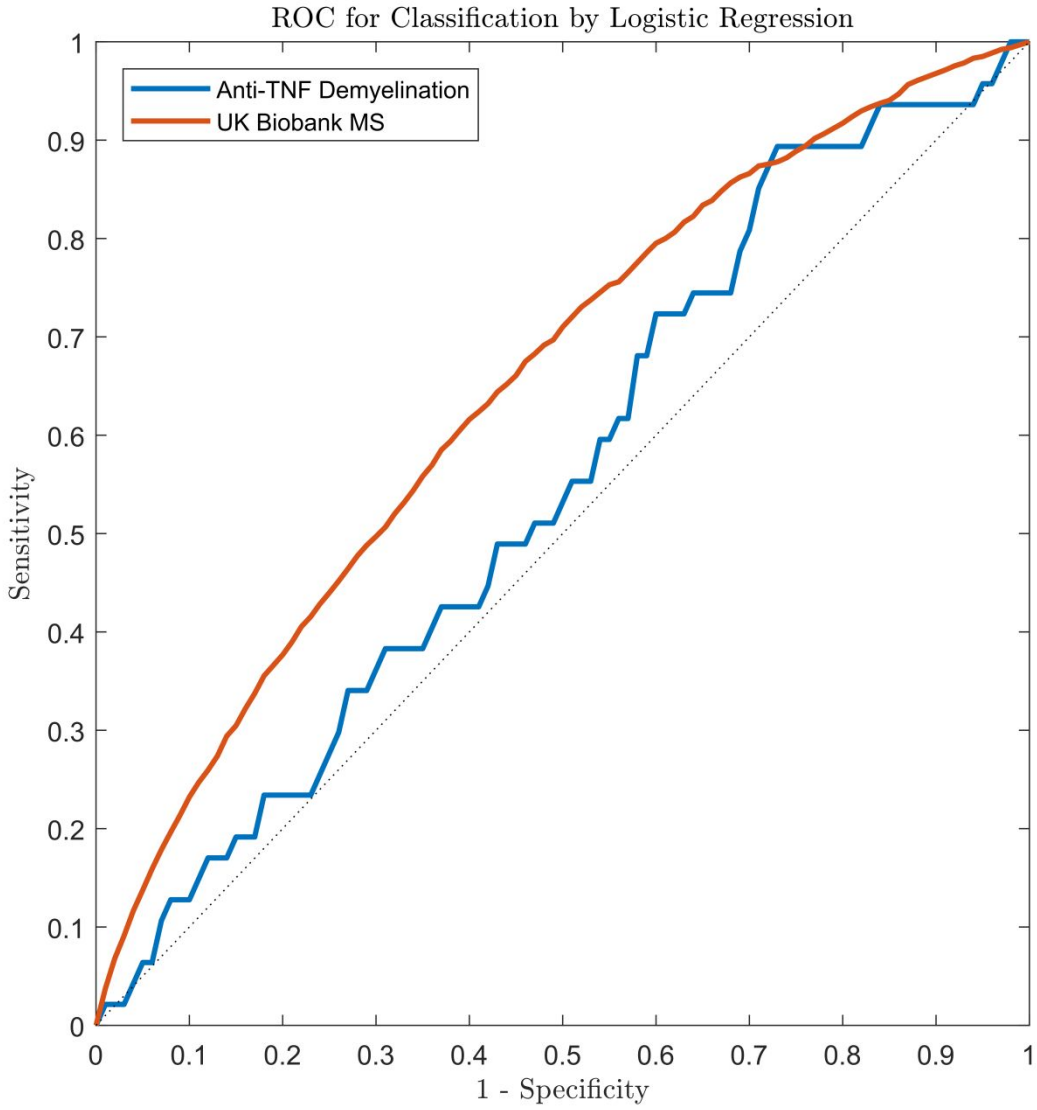

Figure 5. Probability distribution of genetic risk scores (GRS) in cases and controls

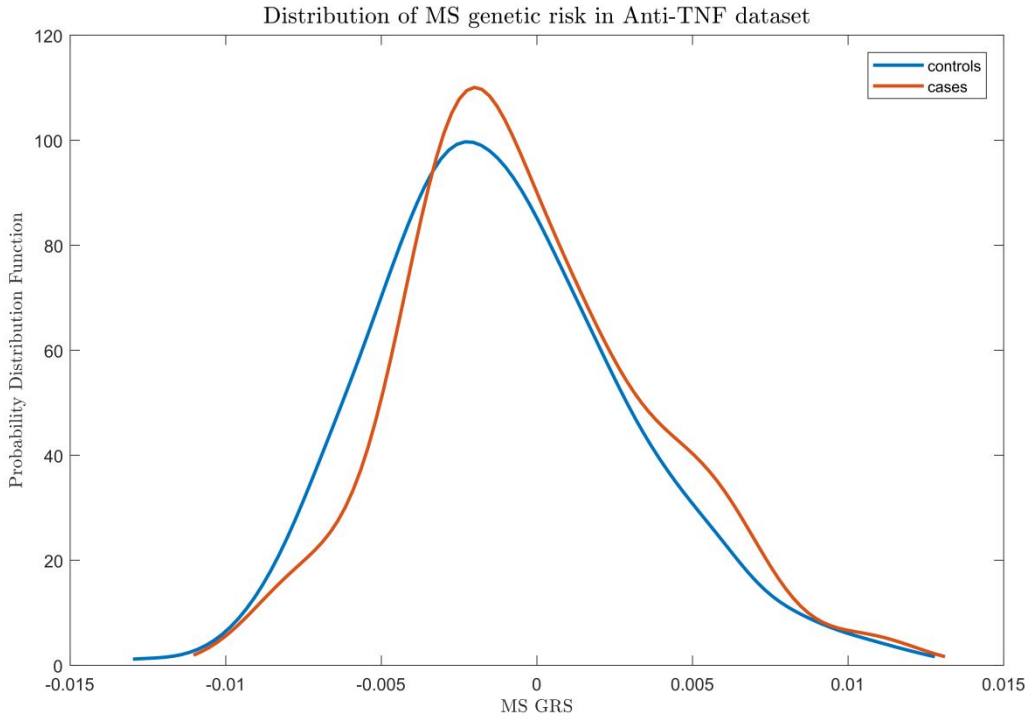

Table 1. Baseline demographic of cases with demyelination related to anti-TNF therapy

Characteristic	**Cases**
Patients, n	**53**
Gender	
Female	39 (73.6%)
Male	14 (26.4%)
Age	
Mean (SD)	40.6 (10.5)
Median [Min, Max]	41.5 [20.7, 63.2]
Ethnicity	
White	44 (83.0%)
Other white background	4 (7.5%)
Mixed white and asian	2 (3.8%)
Any other Asian	2 (3.8%)
Carribean	1 (1.9%)
BMI	
Mean (SD)	25.7 (5.47)
Median [Min, Max]	24.9 [18.0, 43.2]
Missing	5 (9.4%)
Condition	
IBD	32 (60.4%)
RA	12 (22.6%)
Psoriasis	7 (13.2%)
AS	5 (9.4%)
Drug	
Infliximab	25 (47.2%)
Adalimumab	19 (35.8%)
Etanercept	7 (13.2%)
Certrolizumab	1 (1.9%)
Golimumab	1 (1.9%)
Family History	
Yes	5 (9.4%)
No	42 (79.2%)
Smoking	
Current	13 (24.5%)
Ex	13 (24.5%)
Never	21 (39.6%)
Immunomodulator	
Yes	19 (35.8%)
No	34 (64.2%)
Duration on anti-TNF (months)	

Mean (SD)	28.2 (27.7)
Median [Min, Max]	21.3 [0.460, 99.4]

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

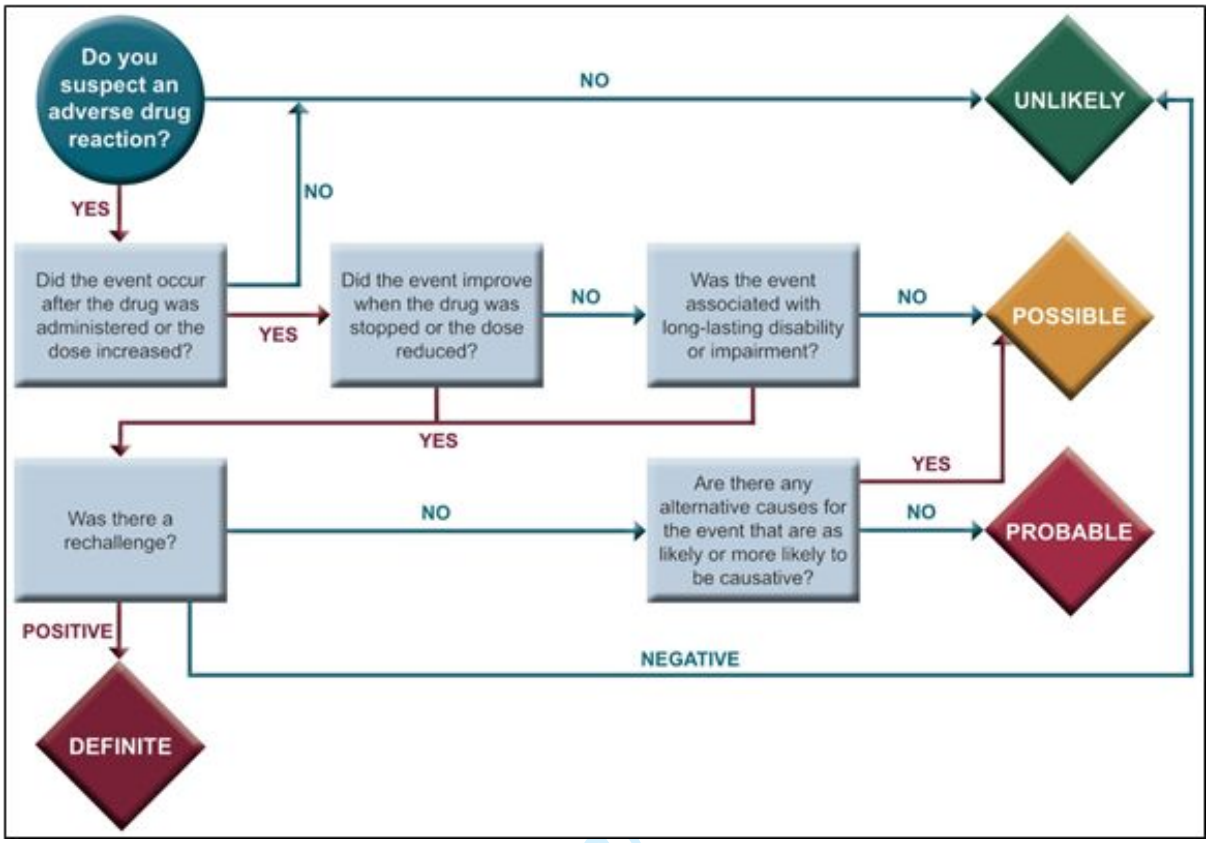
Characteristic (IBD patients)	**Case n = 32**	**Control n = 160**	***p* value**
Sex			
Female	27 (84.4%)	92 (57.5%)	0.008
Male	5 (15.6%)	68 (42.5%)	
Age (median [IQR])	34.1 [29.5, 46.5]	33.9 [25.0, 48.0]	0.542
BMI (median [IQR])	23.6 [20.6, 27.1]	24.1 [20.3, 28.9]	0.539
Smoking			
Current	6 (22.2%)	27 (17.1%)	0.75
Ex	9 (33.3%)	50 (31.6%)	
Never	12 (44.4%)	81 (51.3%)	
Concurrent immunomodulator	10 (31.2%)	89 (55.6%)	0.02

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

Characteristic of demyelination events	Cases (n = 53)
Investigations	
Lumbar puncture	32 (60.4%)
Nerve conduction studies	8 (15.1%)
Electrophysiology	19 (35.8%)
Treatment	
Steroids	21 (39.6%)
IVIG	8 (15.1%)
Plasma exchange	4 (7.5%)
None	24 (45.3%)
Other	1 (1.9%)
Time to recovery (Months)	
Mean (SD)	8.30 (8.54)
Median [Min, Max]	6.75 [0.10, 28.7]
Duration of follow-up (Months)	
Mean (SD)	38.8 (33.7)
Median [Min, Max]	31.0 [2.00, 171]

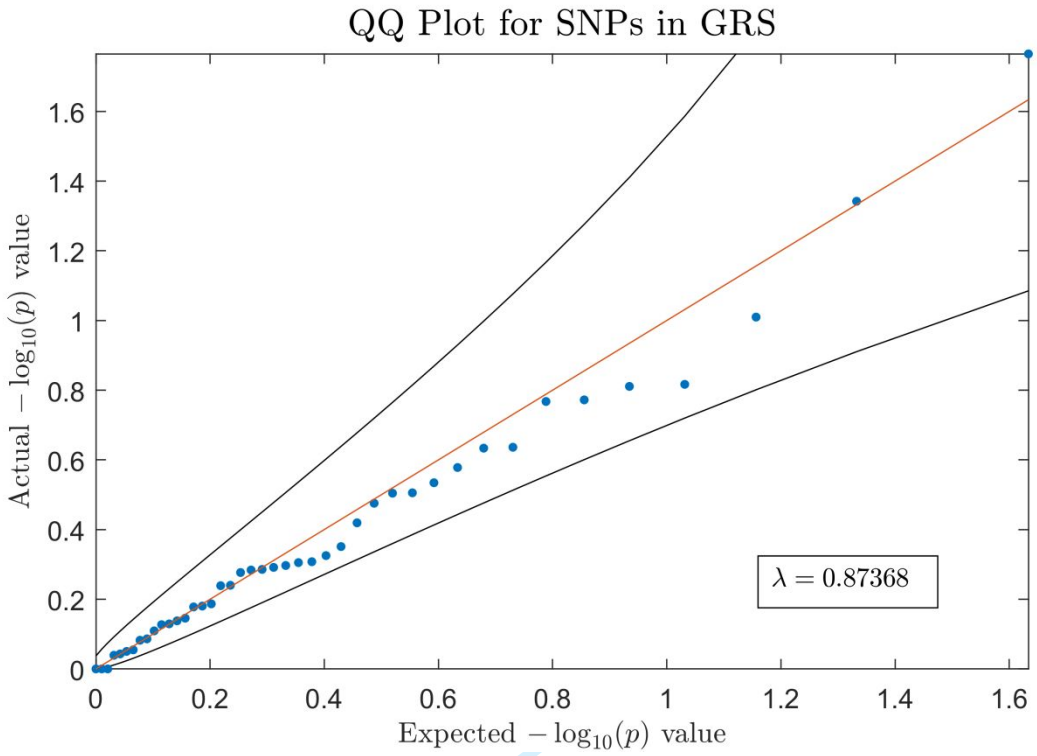
Supplemental – Table of Contents

Supplemental Figure 1. Adjudication assessment tool



Adapted version of the Liverpool Adverse Drug Reaction Causality Assessment Tool used in the adjudication process. Adapted from Gallagher *et al*. (Gallagher, R.M. *et al*. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. *PLoS One*, e28096, 2011).

Supplemental Figure 2. Quantile-Quantile (QQ) plot demonstrating genomic inflation factor of the single nucleotide polymorphisms (SNPs) included in the multiple sclerosis genetic risk score (GRS)



Supplemental Table 1. MS susceptibility loci and their log odds ratio that were used to construct a MS Genetic Risk Score (GRS)

Chromosome: Base Pair	Effect Allele	Log Odds Ratio
6:32119898	A	0.376212
6:27861670	A	0.130655
6:27037080	A	0.114944
6:28413491	G	0.090611
1:85746993	A	0.085647
1:92975464	A	0.078819
2:231115454	C	0.067815
7:37382465	C	0.064832
*3:28078571**	*A*	*0.062206*
17:57816757	A	0.058426
12:6440009	G	0.058426
6:137452908	G	0.056905
7:27014988	C	0.056142
5:176788570	G	0.053463
6:36375304	G	0.052694
8:79575804	A	0.049993
19:16505106	G	0.048053
7:28172739	C	0.048053
11:71168073	A	0.046495
11:60793330	A	0.045714
6:135739355	A	0.04454
3:159691112	G	0.043755
12:9905690	G	0.043362
17:40530763	A	0.041787
8:128192981	G	0.041787
*16:30130493**	*A*	*-0.04062*
5:40399096	A	-0.04177
*11:118724894**	*A*	*-0.0422*
10:94481917	A	-0.04374
2:191974435	A	-0.04455
*7:50325567**	*A*	*-0.04494*
2:61095245	G	-0.04687
5:35879156	A	-0.04803
6:138244816	G	-0.04842
8:128815029	A	-0.04881
1:200874728	G	-0.05037
5:55440730	A	-0.05076
*12:58182062**	*T*	*-0.05537*
19:10742170	A	-0.05576
1:2525665	G	-0.05616
3:121543577	A	-0.05844
6:159470559	A	-0.06068
19:18285944	A	-0.06143
*19:6668972**	*A*	*-0.06596*
1:192541472	G	-0.07043
3:119222456	G	-0.07557

10:6099045	G	-0.08244
16:11194771	A	-0.08386
*14:88432328**	*A*	*-0.11759*
*1:117080166**	*C*	*-0.12709*
6:29904929	C	-0.15808

**denotes Single Nucleotide Polymorphisms (SNP) that failed genetic quality control checks*

Supplemental Table 2. Location, effect allele, frequency and statistics of each individual locus in the MS Genetic Risk Score (GRS) in order of p value

Chromosome	Basepair	Allele 1	Allele frequency of cases	Allele frequency of controls	Allele 2	p- value	Odds Ratio
11	60793330	A	0.5106	0.3827	G	0.01718	1.683
19	18285944	A	0.3723	0.2742	G	0.04549	1.57
17	40530763	A	0.4255	0.3415	G	0.09778	1.428
6	135739355	A	0.4255	0.35	C	0.1525	1.376
6	29904929	C	0.2872	0.3633	A	0.1546	0.7062
3	159691112	G	0.5106	0.4363	A	0.169	1.348
17	57816757	A	0.5426	0.4657	G	0.1708	1.361
5	35879156	A	0.2021	0.2597	C	0.2311	0.7222
1	2525665	G	0.3085	0.371	A	0.2325	0.7565
5	55440730	A	0.1809	0.2323	G	0.2642	0.7298
3	119222456	C	0.2447	0.198	G	0.2922	1.312
5	40399096	A	0.3723	0.321	G	0.3123	1.255
6	138244816	G	0.266	0.2214	A	0.3131	1.274
6	159470559	A	0.4362	0.3871	T	0.3346	1.225
5	176788570	G	0.3085	0.3552	A	0.3808	0.8098
7	28172739	C	0.1809	0.2202	A	0.4455	0.782
6	137452908	G	0.2234	0.2621	A	0.4729	0.8099
7	37382465	C	0.1277	0.1048	A	0.4924	1.25
1	192541472	C	0.1489	0.1827	G	0.4953	0.7831
16	11194771	A	0.2979	0.3343	G	0.5048	0.8449
2	191974435	A	0.3191	0.3548	G	0.5112	0.8523
2	231115454	C	0.234	0.2069	G	0.5181	1.172
19	10742170	A	0.234	0.2081	G	0.5201	1.163
11	71168073	A	0.2447	0.2194	G	0.5288	1.153
6	27037080	A	0.06383	0.08871	G	0.5754	0.7004
2	61095245	G	0.2979	0.3286	A	0.5769	0.8667
1	92975464	A	0.1596	0.1411	G	0.6505	1.156
8	128192981	G	0.3723	0.3488	A	0.66	1.108
12	9905690	G	0.3936	0.3694	A	0.6638	1.108
6	27861670	A	0.07447	0.08992	G	0.7151	0.8143
8	128815029	A	0.2979	0.2827	G	0.7278	1.077
3	121543577	A	0.3723	0.3548	C	0.7425	1.079
10	94481917	A	0.3617	0.3806	G	0.7464	0.922
7	27014988	C	0.1489	0.1665	A	0.7776	0.8758
19	16505106	G	0.3191	0.306	A	0.8198	1.063

6	28413491	G	0.3723	0.3609	A	0.8274	1.051
6	32119898	A	0.1489	0.1448	G	0.8815	1.034
6	36375304	G	0.1809	0.1766	A	0.8907	1.029
10	6099045	G	0.2553	0.2669	A	0.9055	0.9416
12	6440009	G	0.383	0.3758	A	0.9138	1.031
1	85746993	A	0.08511	0.09073	G	1	0.9323
1	200874728	G	0.2766	0.2766	A	1	0.9999
8	79575804	A	0.2447	0.2504	G	1	0.9697

Supplemental Appendix 1. Participants of Adjudication Meetings

Name	Institution
Tariq Ahmad	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Alasdair Coles	Department of Clinical Neurosciences, University of Cambridge, UK
James R. Goodhand	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Timothy Harrower	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Graham A. Heap	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Neel Heerasing	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Peter Hendy	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Jeremy Hobart	Department of Neurology, University Hospitals Plymouth, Plymouth, UK
Nicholas Kennedy	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Simeng Lin	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Roswell Martin	Department of Neurology, Gloucestershire Hospitals NHS Foundation Trust, Gloucester, UK
Gareth J. Walker	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK
Alexander Spiers	Department of Gastroenterology, Royal Devon and Exeter Hospital NHS Foundation Trust, Exeter, UK

Supplemental Appendix 2: PRED4 study group members

Country	Hospital or Trust name	City	Name	Job Title	Highest academic qualification
Australia	Mater Research Institute – University of Queensland	Brisbane	Professor Timothy H Florin	Consultant Gastroenterologist	MBBS
Australia	Canberra Hospital	Canberra	Dr Kavitha Subramaniam	Consultant Gastroenterologist	MBBS
Canada	University of Alberta	Edmonton	Dr Richard N Fedorak	Professor of Medicine in Gastroenterology	MD
Canada	Mount Sinai Hospital	Toronto	Dr Mark Silverberg	Consultant Gastroenterologist	PhD
Denmark	Hospital of Southern Jutland	Jutland	Professor Vibeke Andersen	Clinical Professor	MD
United Kingdom	Aberdeen Royal Infirmary, NHS Grampian	Aberdeen	Dr Malcolm Smith	Consultant Gastroenterologist	MBChB
United Kingdom	Stoke Mandeville Hospital	Aylesbury	Dr David Gorard	Consultant Gastroenterologist	MD
United Kingdom	Northern Devon Healthcare Trust	Barnstaple	Dr Alex Moran	Consultant Gastroenterologist	MD
United Kingdom	Heart of England NHS Foundation Trust	Birmingham	Dr Naveen Sharma	Consultant Gastroenterologist	PhD
United Kingdom	Queen Elizabeth Hospital	Birmingham	Dr Tariq Iqbal	Consultant Gastroenterologist	MD
United Kingdom	University of Cambridge	Cambridge	Professor Alasdair Coles	Professor of Neuroimmunology	PhD
United Kingdom	Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust	Cambridge	Dr Miles Parkes	Consultant Gastroenterologist	DM
United Kingdom	Western General Hospital, NHS Lothian	Edinburgh	Dr Charlie W Lees	Consultant Gastroenterologist	PhD
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Tariq Ahmad	Consultant Gastroenterologist	DPhil
United Kingdom	Royal Devon and Exeter Hospital NHS Foundation Trust	Exeter	Dr Neil Chanchlani	IBD Research Fellow	MBChB
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr James R Goodhand	Consultant Gastroenterologist	MBBS
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Benjamin Hamilton	IBD Research Fellow	MBBS
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Timothy Harrower	Consultant Neurologist	PhD
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Graham A Heap	IBD Research Fellow	PhD
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Neel M Heerasing	IBD Research Fellow	MBBS
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Peter Hendy	IBD Research Fellow	MBBS
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Nicholas A Kennedy	Consultant Gastroenterologist	MBBS

United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Simeng Lin	IBD Research Fellow	MBChB
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Alexander Spiers	Consultant Radiologist	BMBCh
United Kingdom	Royal Devon and Exeter NHS Foundation Trust	Exeter	Dr Gareth J Walker	IBD Research Fellow	PhD
United Kingdom	University of Exeter	Exeter	Ms Claire M Bewshea	Group Manager	MSC
United Kingdom	University of Exeter	Exeter	Mrs Hanlie Olivier	Research Administrator	MATRIC
United Kingdom	University of Exeter Medical School	Exeter	Dr Harry D Green	Postdoctoral Research Fellow	PhD
United Kingdom	University of Exeter Medical School	Exeter	Dr Michael Weedon	Associate Professor in Genetics	PhD
United Kingdom	Glasgow Royal Infirmary, NHS Greater Glasgow and Clyde	Glasgow	Dr Daniel R Gaya	Consultant Gastroenterologist	MD
United Kingdom	Royal Hospital for Children, NHS Greater Glasgow and Clyde	Glasgow	Professor Richard K Russell	Consultant Paediatric Gastroenterologist	PhD
United Kingdom	Gloucestershire Royal Hospital, Gloucestershire Hospitals NHS Foundation Trust	Gloucester	Dr Paul Dunckley	Consultant Gastroenterologist	DPhil
United Kingdom	Gloucestershire Royal Hospital, Gloucestershire Hospitals NHS Foundation Trust	Gloucester	Dr Roswell J Martin	Consultant Neurologist	MD
United Kingdom	Harrogate and District NHS Foundation Trust	Harrogate	Dr Joanne Ridpath	Consultant Gastroenterologist	BM
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United Kingdom	Airedale NHS Foundation Trust	Keighley	Dr Richard Shenderay	Consultant Gastroenterologist	MBBS
United Kingdom	East Kent Hospitals University NHS Foundation Trust	Kent	Dr Michael P Delaney	Consultant Nephrologist	MD
United Kingdom	Royal Liverpool and Broadgreen University Hospital NHS Trust	Liverpool	Dr Sreedhar Subramanian	Consultant Gastroenterologist	MD
United Kingdom	Guy's and St Thomas' Hospital NHS Foundation Trust	London	Dr Peter M Irving	Consultant Gastroenterologist	MD
United Kingdom	King's College Hospital	London	Dr Guy Chung-Faye	Consultant Gastroenterologist	PhD
United Kingdom	Royal Free Hospital, Royal Free London NHS Foundation Trust	London	Dr Charles Murray	Consultant Gastroenterologist	PhD
United Kingdom	University College London Hospitals	London	Dr Stuart Bloom	Consultant Gastroenterologist	DM
United Kingdom	Royal Victoria Infirmary, Newcastle Upon Tyne Hospitals NHS Foundation Trust	Newcastle upon Tyne	Dr John C Mansfield	Consultant Gastroenterologist	MD

United Kingdom	Oxford University Hospitals	Oxford	Professor Alison Simmons	Consultant Gastroenterologist	PhD
United Kingdom	Derriford Hospital, University Hospitals Plymouth NHS Trust	Plymouth	Professor Jeremy Hobart	Consultant Neurologist	PhD
United Kingdom	Royal Berkshire Hospital	Reading	Dr Jonathan D Simmons	Consultant Gastroenterologist	DM
United Kingdom	Salford Royal NHS Foundation Trust	Salford	Professor Simon Lal	Consultant Gastroenterologist	PhD
United Kingdom	Royal Hallamshire Hospital	Sheffield	Professor Alan Lobo	Consultant Gastroenterologist	MD
United Kingdom	Southampton General Hospital	Southampton	Dr Richard Felwick	Consultant Gastroenterologist	PhD
United Kingdom	Southampton General Hospital	Southampton	Dr JR Fraser Cummings	Consultant Gastroenterologist	DPhil
United Kingdom	Musgrove Park Hospital, Taunton and Somerset NHS Foundation Trust	Taunton	Dr Emma R Greig	Consultant Gastroenterologist	PhD
United Kingdom	Torbay and South Devon NHS Foundation Trust	Torquay	Dr Mark Feeney	Consultant Gastroenterologist	MD
United Kingdom	Royal Cornwall Hospital Trust	Truro	Dr John Beckly	Consultant Gastroenterologist	MD
United Kingdom	The Mid Yorkshire Hospitals NHS Trust	Wakefield	Dr Deven Vani	Consultant Gastroenterologist	MD
United Kingdom	New Cross Hospital, The Royal Wolverhampton Hospitals NHS Trust	Wolverhampton	Dr Matthew J Brookes	Consultant Gastroenterologist	PhD
United Kingdom	Worthing Hospital, Western Sussex Hospitals	Worthing	Dr Zinu Philipose	Consultant Gastroenterologist	MBBS
United Kingdom	Yeovil District Hospital	Yeovil	Dr Steve Core	Consultant Gastroenterologist	MD

Supplemental Appendix 3. Case Report Form

International IBD Genetics Consortium

PRED4

Anti-TNFα Induced Demyelination

Case Report Form

Please stick study label here

On completion, please return to:
IBD Pharmacogenetics Research Office
The Research, Innovation, Learning and Development Centre (RILD)
Barrack Road
Exeter
EX2 5DW

Anti-TNFα Induced Demyelination
Introduction

Please complete all boxes where indicated and in black ball point pen.

If you make a mistake please put a line through the box, initial and date and write answer to the side.

Complete dates in format dd/mm/yyyy

The patient identification number is the bar code on the front of the CRF. Please transcribe this on to the top of the page in each relevant section.

For study inclusion participants must meet all the major criteria and any number of the additional minor criteria.

***Other potential causes of neurological symptoms**

Acute disseminated encephalomyelitis (ADEM), Behcet's disease, polyarteritis nodosa, Sjögren's disease, anti-phospholipid syndrome, systemic lupus erythematosus (SLE), sarcoid, Infections (such as HIV, Lyme, neurosyphilis, Listeria, Progressive multifocal leukoencephalopathy [PML]), Vitamin B12 deficiency

This study covers both central nervous system (CNS) and peripheral nervous system (PNS) demyelination.

Anti-TNFα Induced Demyelination

Section 1 - Inclusion Criteria

Study code ☐

1.1 Major criteria (all must be met)

- ☐ History of exposure to anti-TNFα antibody at any time in the past
- ☐ No history of demyelinating neurological symptoms prior to exposure to Anti-TNFα antibody
- ☐ Neurological symptoms lasting at least 24 hours
- ☐ MRI brain and/or spinal cord shows changes consistent with CNS demyelination; or electrophysiological tests (nerve conduction or evoked potentials) are consistent with PNS or CNS demyelination.
- ☐ CNS or PNS inflammatory demyelination confirmed by Neurologist
- ☐ Neurological opinion implicates anti-TNFα medication as possible cause of demyelination, and if the patient is still receiving the drug, it is withdrawn

1.2 Other potential causes for neurological symptoms (see page 2)*

- ☐ No - Category A
- ☐ Yes - Category B

If yes, please specify ☐

1.3 Minor criteria:

- ☐ Resolution (partial or complete) of symptoms on drug withdrawal (with or without specific treatment)
- ☐ Recurrence of symptoms on re-challenge with anti-TNFα antibody

1.4 Number of minor criteria ☐

1.5 Participant's eligibility Investigator sign-off

Is the participant eligible to take part in the clinical trial? ☐ Yes ☐ No

If no, please give reason(s) for screen failure:

1.
2.
3.

Investigator's signature ☐ Date ☐ dd / mm / yyyy

Investigator's name (print) ☐

Anti-TNFα Induced Demyelination

Section 2 - Patient Details

Study code

2.1 Patient details

Date of Birth dd / mm / yyyy Sex: M ☐ F ☐

Weight at time of initial anti-TNFα dose (or nearest weight) kg

Height cm

2.2 Ethnicity - *Please tick as appropriate*

White

- ☐ British
- ☐ Irish
- ☐ Any other White background

Black or Black British

- ☐ Caribbean
- ☐ African
- ☐ Any other Black background

Mixed

- ☐ White and Black Caribbean
- ☐ White and Black African
- ☐ White and Asian
- ☐ Any other Mixed background

Chinese or Other Ethnic Group

- ☐ Chinese
- ☐ Any other ethnic group (*please specify*)
- ☐ Not stated

Asian or Asian background

- ☐ Indian
- ☐ Pakistani
- ☐ Bangladeshi
- ☐ Any other Asian background

2.3 Participant informed consent

Date participant signed written consent form dd / mm / yyyy

Date of blood sample taken dd / mm / yyyy

Anti-TNFα Induced Demyelination

Section 3 - Medical History

Study code

3.1 Hospital Details

3.1.1 Consultant Gastroenterologist/ Rheumatologist/Dermatologist

Hospital

Hospital address

Consultant telephone

Consultant email

3.1.2 Consultant Neurologist

Hospital

Hospital address

Consultant telephone

Consultant email

3.2 Medical History

3.2.1 Indication for Anti-TNFα medication:

- ☐ Inflammatory bowel disease – Crohn's Disease/Ulcerative Colitis
- ☐ Rheumatoid Arthritis
- ☐ Ankylosing Spondylitis
- ☐ Seronegative spondyloarthropathies
- ☐ Psoriasis
- ☐ Other, please specify:

3.3 Comorbidities ☐ Yes ☐ No

3.3.1 Hypertension ☐ Yes ☐ No Date of diagnosis dd / mm / yyyy

3.3.2 Diabetes ☐ Yes ☐ No Date of diagnosis dd / mm / yyyy

- ☐ Type I — Using insulin: ☐ Yes ☐ No
- ☐ Type II — Date commenced insulin dd / mm / yyyy

Anti-TNFα Induced Demyelination

Section 3 - Medical History

Study code

3.3.3 Severe peripheral vascular disease ☐ Yes ☐ No

Date of diagnosis dd / mm / yyyy

3.3.4 Myocardial infarction ☐ Yes ☐ No

Date of diagnosis dd / mm / yyyy

3.3.5 TIA/CVA ☐ Yes ☐ No

Date of diagnosis dd / mm / yyyy

3.4 Other significant medical history ☐ Yes ☐ No

If yes, please give details here

3.5 Smoking History

3.5.1 ☐ Never Smoked ☐ Ex Smoker ☐ Current Smoker

3.5.2 Start Date dd / mm / yyyy

3.5.3 End Date dd / mm / yyyy

3.5.4 Maximum number of cigarettes per day

Anti-TNFα Induced Demyelination

Section 4 - Anti-TNFα History

Study code

4.1 Anti-TNFα Medication

	Date Anti-TNFα Medication commenced	Date Anti-TNFα Medication ceased	Dose of Anti-TNFα Medication	Number of doses
Infliximab	dd / mm / yyyy	dd / mm / yyyy		
Adalimumab	dd / mm / yyyy	dd / mm / yyyy		
Certolizumab pegol	dd / mm / yyyy	dd / mm / yyyy		
Etanercept	dd / mm / yyyy	dd / mm / yyyy		
Other, please specify	dd / mm / yyyy	dd / mm / yyyy		

4.2 Date of onset of neurological symptoms

dd / mm / yyyy

4.3 Please describe the patient's symptoms

4.4 Please describe the neurological examination findings

Anti-TNFα Induced Demyelination

Section 4 - Anti-TNFα History

Study code

4.5 Had the patient ever had an MRI brain and/or spinal cord BEFORE the onset of this episode

☐ Yes ☐ No ☐ Unknown

If yes what was the date of this scan dd / mm / yyyy

Was a contrast agent used? ☐ Yes ☐ No ☐ Unknown

If yes, please specify

Please copy report text below or attach photocopy of report after anonymisation

4.6 Did the patient have an MRI Brain and/or spinal cord AFTER the onset of neurological symptoms?

☐ Yes ☐ No ☐ Unknown

If yes what was the date of this scan dd / mm / yyyy

Was a contrast agent used? ☐ Yes ☐ No ☐ Unknown

If yes, please specify

Please copy report text below or attach photocopy of report after anonymisation

Anti-TNFα Induced Demyelination

Section 4 - Anti-TNFα History

Study code

4.7 Did the patient have a lumbar puncture/CSF examination?

☐ Yes ☐ No ☐ Unknown

If yes, please give findings or attach photocopy of report after anonymisation

4.8 Did the patient have evoked potentials (EP) carried out - Visual (VEP), Somatosensory (SSEP) or Brainstem Auditory (BAEP)?

☐ Yes ☐ No ☐ Unknown

Please copy report text below or attach photocopy of report after anonymisation

4.9 Did the patient have nerve conducting studies?

☐ Yes ☐ No ☐ Unknown

Please copy report text below or attach photocopy of report after anonymisation

4.10 Did the patient have any other investigations?

☐ Yes ☐ No ☐ Unknown

If yes, please give details

Anti-TNFα Induced Demyelination

Section 4 - Anti-TNFα History

Study code

4.11 Did the patient require hospital admission?

☐ Yes ☐ No ☐ Unknown

If yes: Date of admission dd / mm / yyyy

Date of discharge dd / mm / yyyy

4.12 Did the patient require any specific treatment?

☐ Yes ☐ No ☐ Unknown

If yes, what treatment was given?

☐ Intravenous Immunoglobulin (IVIG)

☐ Steroids

☐ Plasma exchange

☐ Other, please specify

4.13 Disease course (please tick one of the following)

☐ Episode of demyelination with **complete** resolution of symptoms

How long did it take for symptoms to resolve (days)?

☐ Episode of demyelination with **partial** or **no** resolution of symptoms

☐ Relapse-remitting episodes, characterised by further acute symptoms of demyelination

☐ Progressive symptoms

4.14 Was the patient rechallenged with the same or another anti-TNFα agent?

☐ Yes ☐ No ☐ Unknown

If yes: Which anti-TNFα was used?

Date started dd / mm / yyyy Dose and frequency

Did symptoms recur? ☐ Yes ☐ No ☐ Unknown

If Yes Date of recurrence dd / mm / yyyy

Details

Date of Drug withdrawal dd / mm / yyyy

4.15 Family history of multiple sclerosis or peripheral nerve disorder?

☐ Yes ☐ No ☐ Unknown

If yes, please give details

Anti-TNFα Induced Demyelination

Section 4 - Anti-TNFα History

Study code

4.16 Family history of anti-TNFα induced demyelination?

☐ Yes ☐ No ☐ Unknown

If yes, please give details

Section 5 - Other Drug History

(in the last 3 months prior to development of neurological symptoms)

Drug name	Dose and Route	Start date	Stop date
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
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		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy
		dd / mm / yyyy	dd / mm / yyyy

Anti-TNFα Induced Demyelination

Section 6 - Principal Investigator Statement Study code

I have reviewed this CRF and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant. All entries were made either by myself or by a person under my supervision who has signed the Delegation Log.

Principal Investigator's signature

Date dd / mm / yyyy

Principal Investigator's name (print)

ONCE SIGNED, NO FURTHER CHANGES CAN BE MADE TO THIS CRF WITHOUT A SIGNED DATA QUERY FORM