Queen Mary University of London

ATTACK MS

NCT05418010

Natalizumab for the treatment of people with inflammatory demyelination suggestive of multiple sclerosis, or definite multiple sclerosis, at first presentation

Contact: **bartshealth.attackms@nhs.net**

CI: Professor Klaus Schmierer

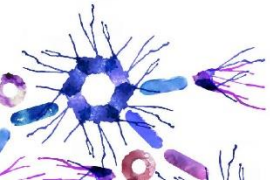
IRAS project 1003822

EudraCT No 2021-002255-11

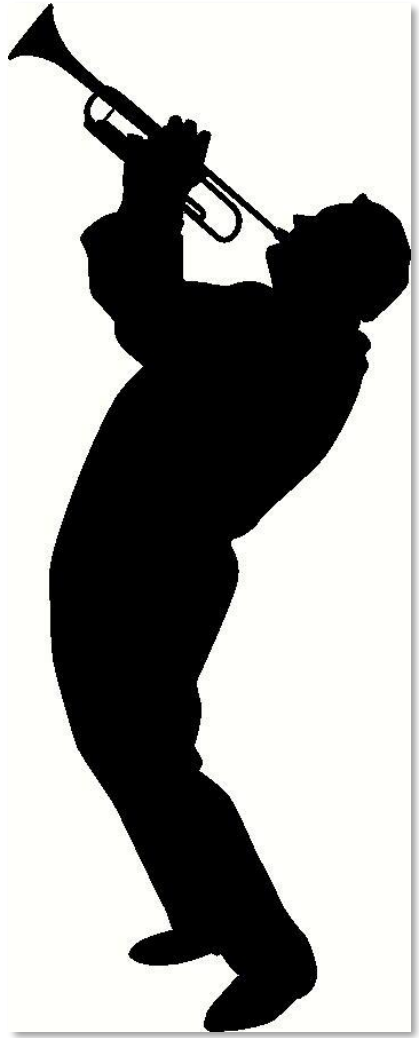
PCTU Pragmatic Clinical Trials Unit

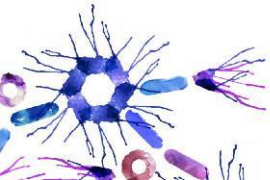
Prevention

- Primary: intervening before health effects occur, through measures such as vaccinations & altering behaviours
- Secondary: people in whom disease has begun but who have not yet developed significant clinical signs and symptoms
- Tertiary: preventing deterioration in those who have developed signs and symptoms of disease



“Treat early”





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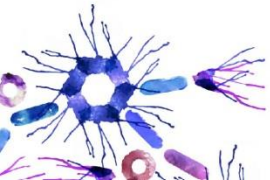
Rationale

- Early treatment has long term benefits – but how early is early?
- Can we change current practice to facilitate brain health? (outcome)
- Is highly effective anti-inflammatory treatment an effective way to remyelinate? (outcome)
- Which compound is most useful in such acute scenario and has no license for the indication *clinically isolated syndrome* (funding)



Timing of high-efficacy therapy for multiple sclerosis: a retrospective observational cohort study

Anna He, Bernd Merkel, James William L Brown, Lana Zhovits Ryerson, Ilya Kister, Charles B Malpas, Sifat Sharmin, Dana Horakova, Eva Kubala Havrdova, Tim Spelman, Guillermo Izquierdo, Sara Eichau, Maria Trojano, Alessandra Lugaresi, Raymond Hupperts, Patrizia Sola, Diana Ferraro, Jan Lycke, Francois Grand'Maison, Alexandre Prat, Marc Girard, Pierre Duquette, Catherine Larochelle, Anders Svenningsson, Thor Petersen, Pierre Grammond, Franco Granella, Vincent Van Pesch, Roberto Bergamaschi, Christopher McGuigan, Alasdair Coles, Jan Hillert, Fredrik Piehl, Helmut Butzkueven, Tomas Kalincik, on behalf of the MSBase study group*

Summary DMTs: rituximab, ocrelizumab, mitoxantrone, alemtuzumab, natalizumab

Background High-efficacy therapies in multiple sclerosis are traditionally used after unsuccessful treatment with first-

Lancet Neurol 2020; 19:307-16

REVIEW

Curr Opin Neurol 2021;34:286-94.

Highly effective disease-modifying treatment as initial MS therapy

Klaus Schmierer[a,b], *Per Soelberg Sorensen*[c,d], *and David Baker*[a]

Purpose of review
Using highly effective (HE) compounds right from the beginning of disease-modifying immunotherapy (DMT) in people with multiple sclerosis (pwMS) has gained popularity among clinicians and pwMS alike. We discuss the most recent evidence supporting this approach, and whether any of the associated risks should stop us adopting it as a default strategy.

Recent findings
With the addition of injectable ofatumumab, and the two oral sphingosines one phosphate modulators siponimod and ozanimod, ten HE DMTs are now available for pwMS, though variation in licensing status and cost may limit their use in some healthcare environments. Real World evidence based on large MS registry data suggests the superiority of early HE DMT over a slow treatment escalation approach; delaying HE DMT leads to more rapid and often irreversible disability accrual. Mechanistically, B-cell depletion, particularly memory B-cell suppression, is a common denominator closely associated with DMT efficacy.

Summary
The concept that HE DMTs are necessarily associated with a high risk of adverse effects, is no longer supported by the evidence. The rather predictable and manageable risk profile of most HE DMTs should lower the threshold for clinicians to discuss such treatment with pwMS as a first line approach.

Keywords
disease-modifying therapy, memory B cells, multiple sclerosis, treatment algorithm

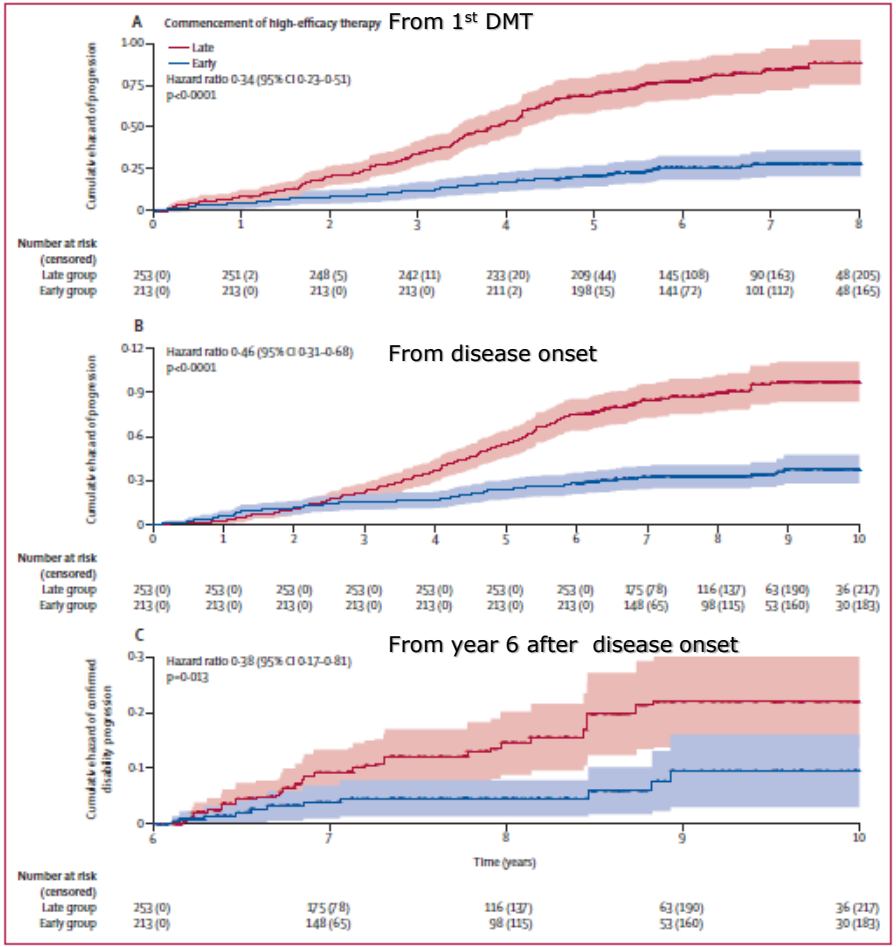
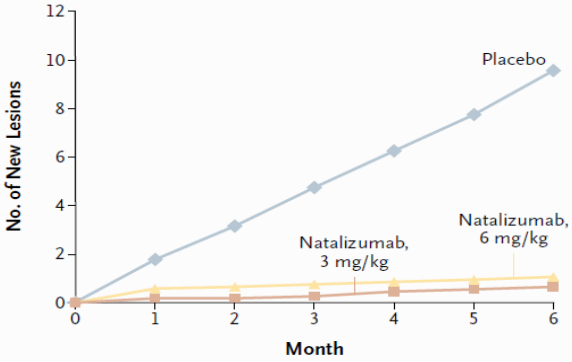


Figure 3: Cumulative hazard of confirmed disability progression in patients with relapsing-remitting multiple sclerosis treated early versus late with high-efficacy therapy
(A) Measured from commencement of first disease-modifying therapy. (B) Measured from disease onset. (C) Measured from year 6 after disease onset. Bold lines are cumulative hazard estimates and shaded areas are 95% CIs.

Blocking the adaptive immune-response from the CNS inhibits MS

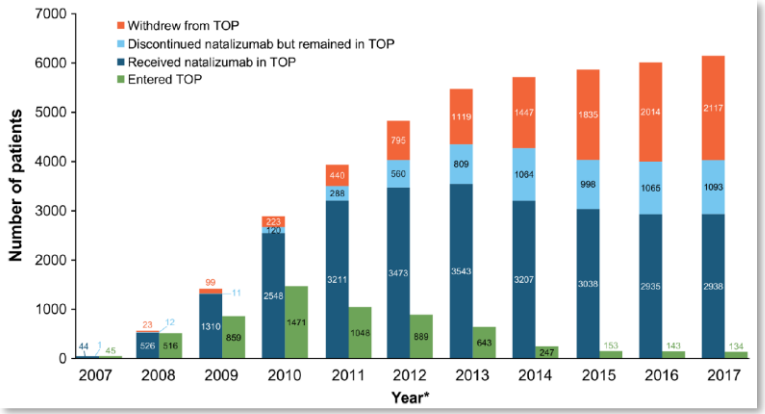


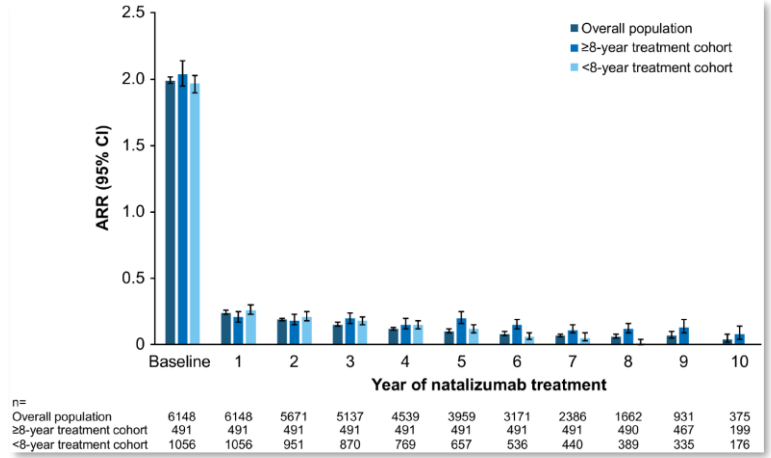
No. with Data							
Placebo	71	68	66	65	66	62	64
Natalizumab, 3 mg/kg	68	66	66	67	65	66	66
Natalizumab, 6 mg/kg	74	73	70	67	68	66	66

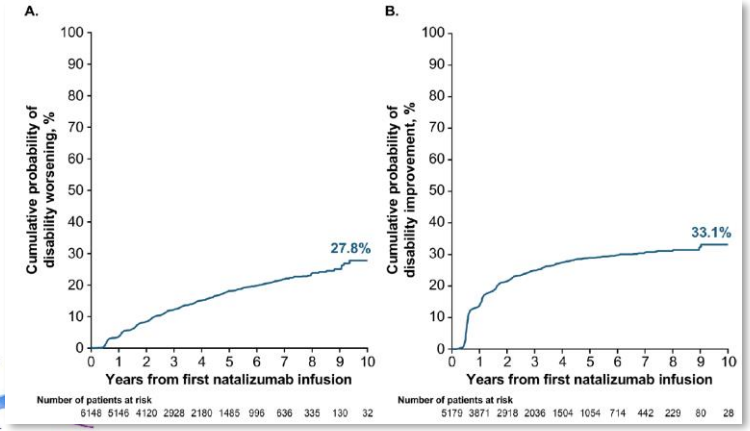
Figure 1. Cumulative Mean Number of New Gadolinium-Enhancing Lesions on MRI in Each Group during Treatment.

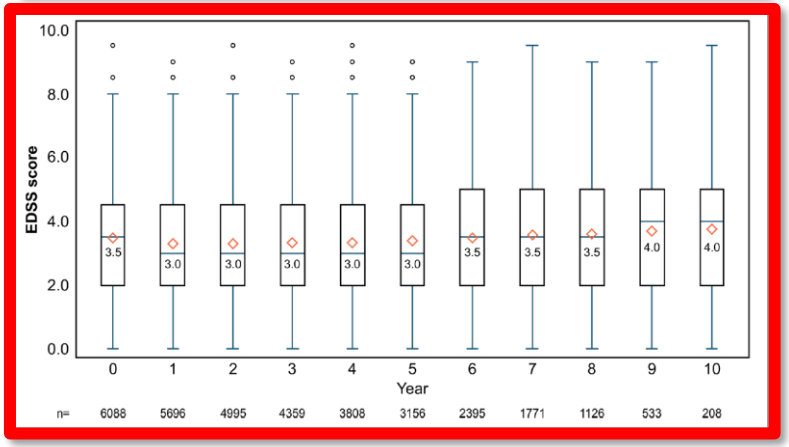
Miller, et al N Engl J Med 2003;348:15-23.

Blocking the adaptive immune-response from the CNS inhibits MS





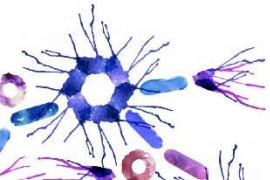




Butzkueven, et al. J Neurol Neurosurg Psychiatry 2020;91:660–8.

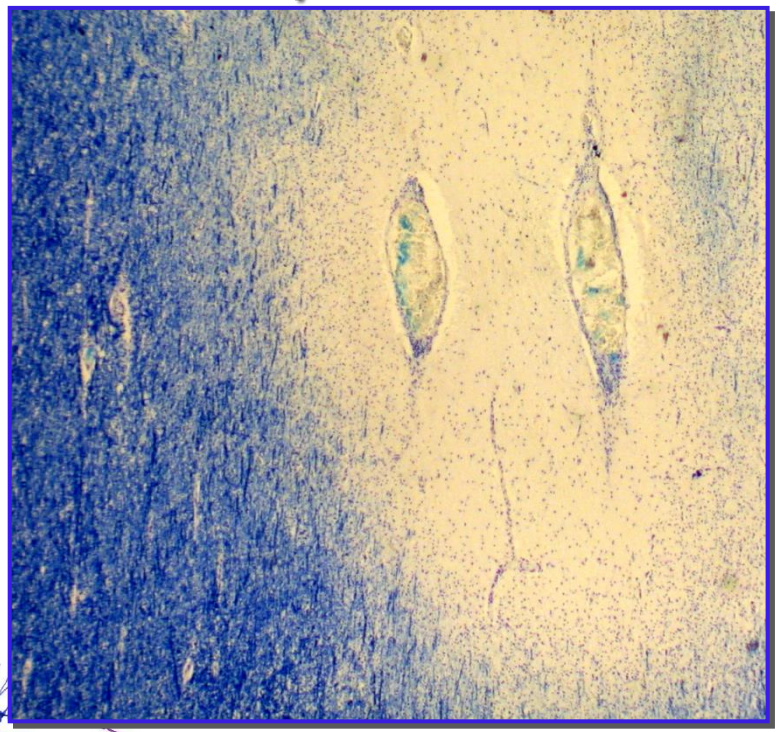
Primary endpoint

- Mean magnetisation transfer ratio (MTR) change in fluid attenuated inversion recovery (FLAIR)-hyper-intense lesions at 12 weeks compared to baseline.

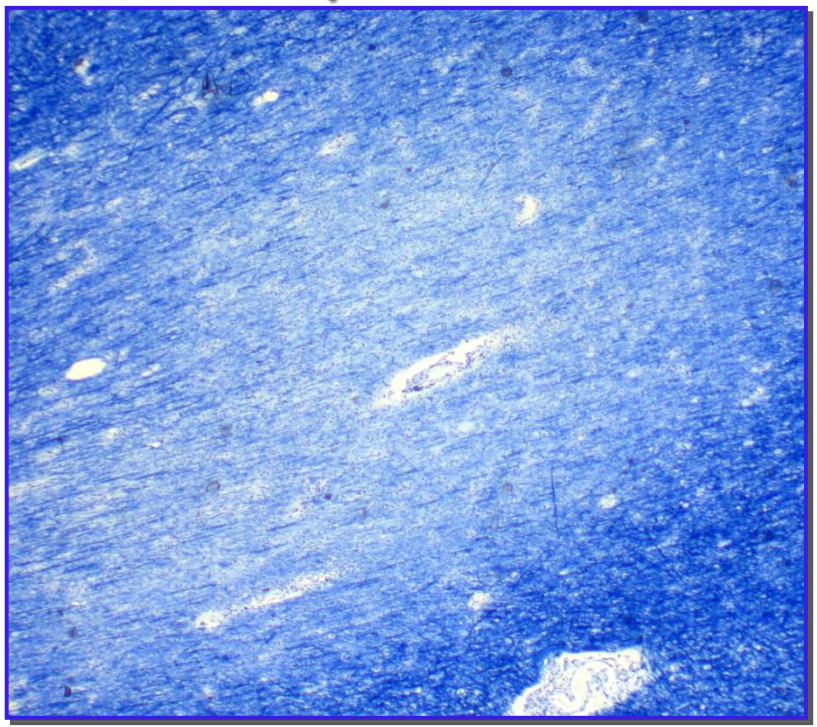


Remyelination in MS

Demyelinated



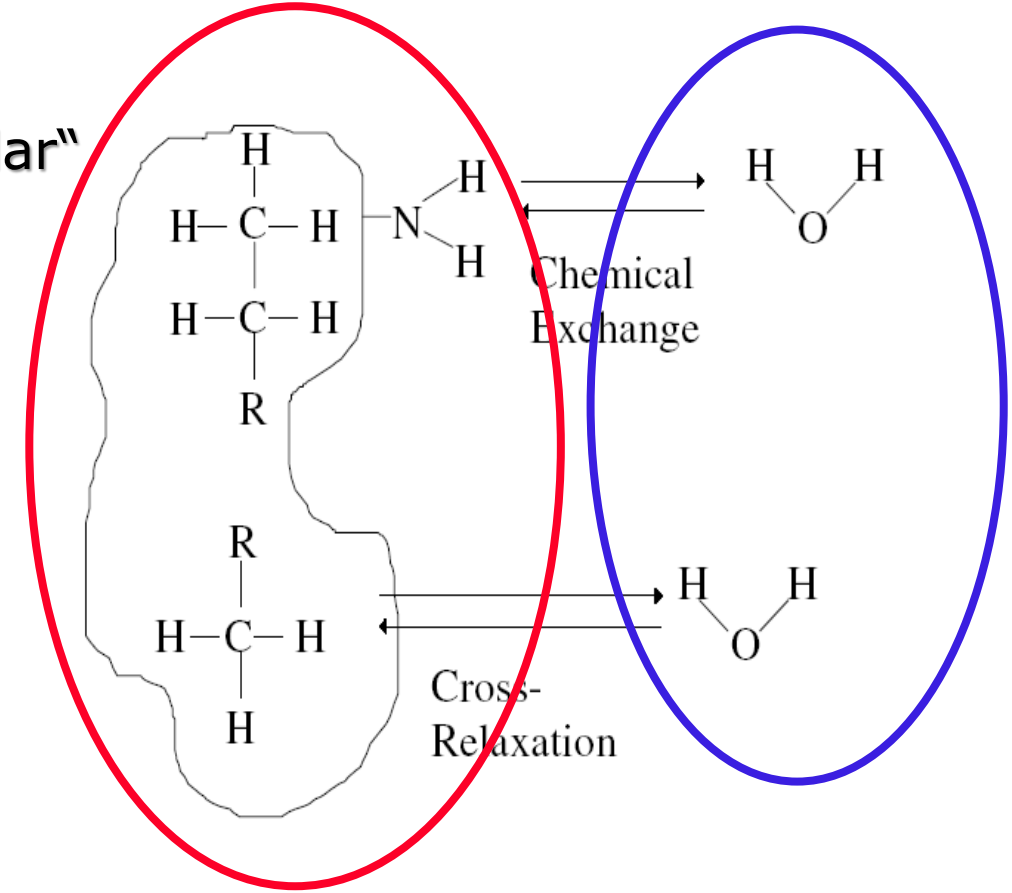
Remyelinated



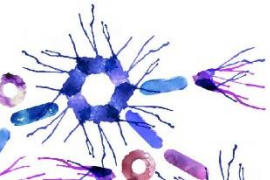
Schmierer K, et al. Ann Neurol 2004

Magnetization transfer

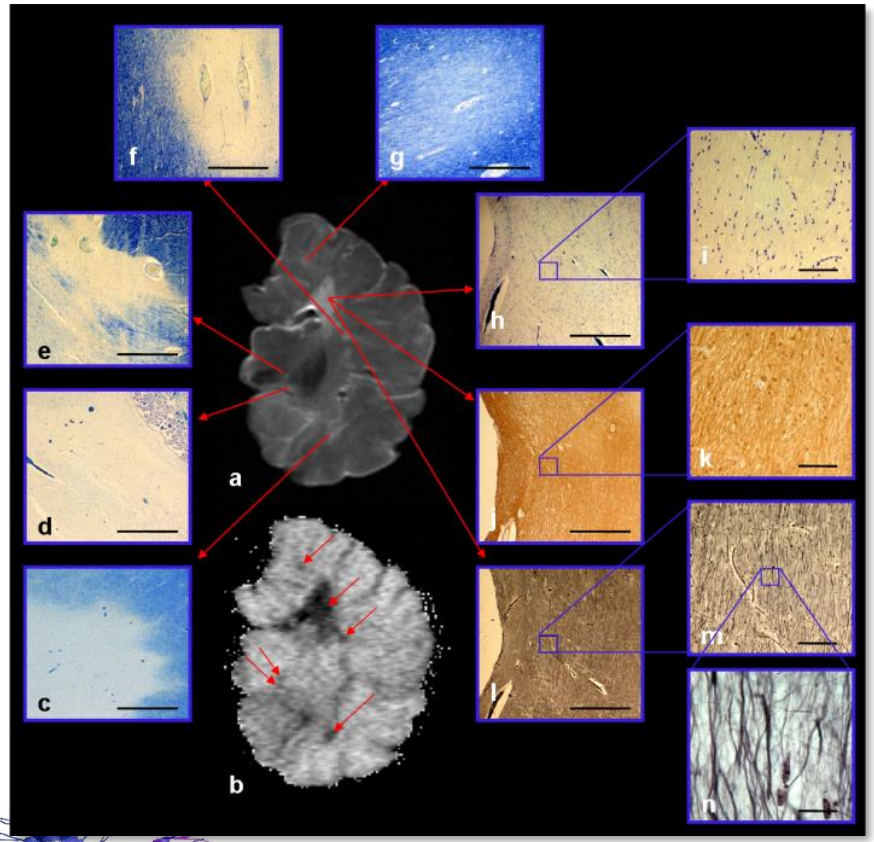
Semisolid pool
"macromolecular"
protons



Liquid pool
"free" protons

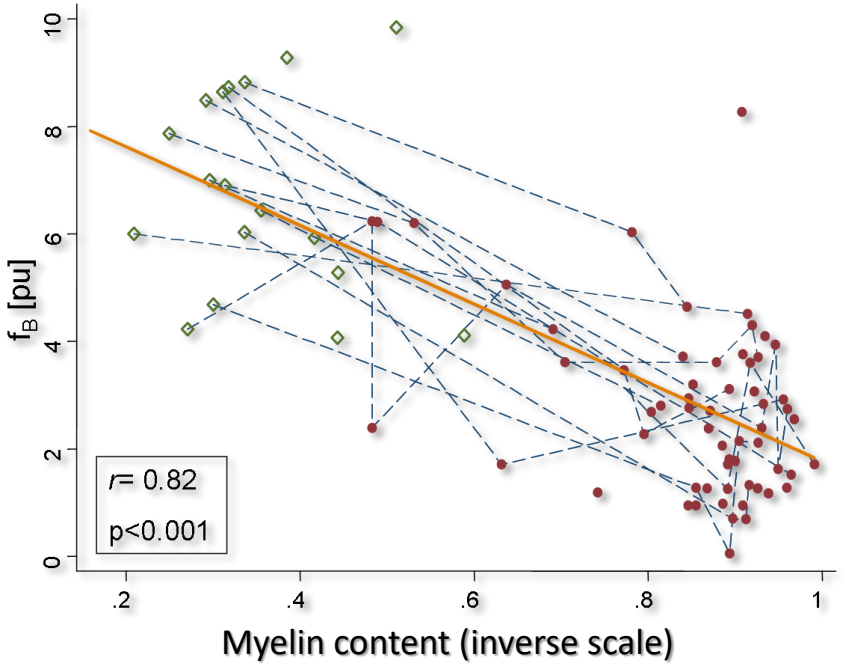


MTR & histology



Schmierer, et al. Ann Neurol 2004 & JMRI 2007

n= 37 pwMS (29 women, 8 men)
Age= 59 years (SD, 13)
Disease duration 27 years (SD, 12).
Retrieval within 15 hours (SD, 8 h) *post mortem*
Time between death and MRI= 43 hours (SD, 22h).



Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/msard

Sample sizes for lesion magnetisation transfer ratio outcomes in remyelination trials for multiple sclerosis

D.R. Altmann[a,b,*,1,2], T. Button[c,1], K. Schmierer[a,d], K. Hunter[a], D.J. Tozer[a], C.A. Wheeler-Kingshott[a], A. Coles[c], D.H. Miller[a]

[a]*Nuclear Magnetic Resonance (NMR) Research Unit, Queen Square Multiple Sclerosis Centre, UCL Institute of Neurology, London, UK*
[b]*Medical Statistics Department, London School of Hygiene & Tropical Medicine (LSHTM), Keppel Street, London WC1E 7HT, UK*
[c]*Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK*
[d]*Blizard Institute, Centre for Neuroscience & Trauma, Barts and The London School of Medicine & Dentistry, London, UK*

Mult Scler Relat Disord 2014;3:237-43.

Overview

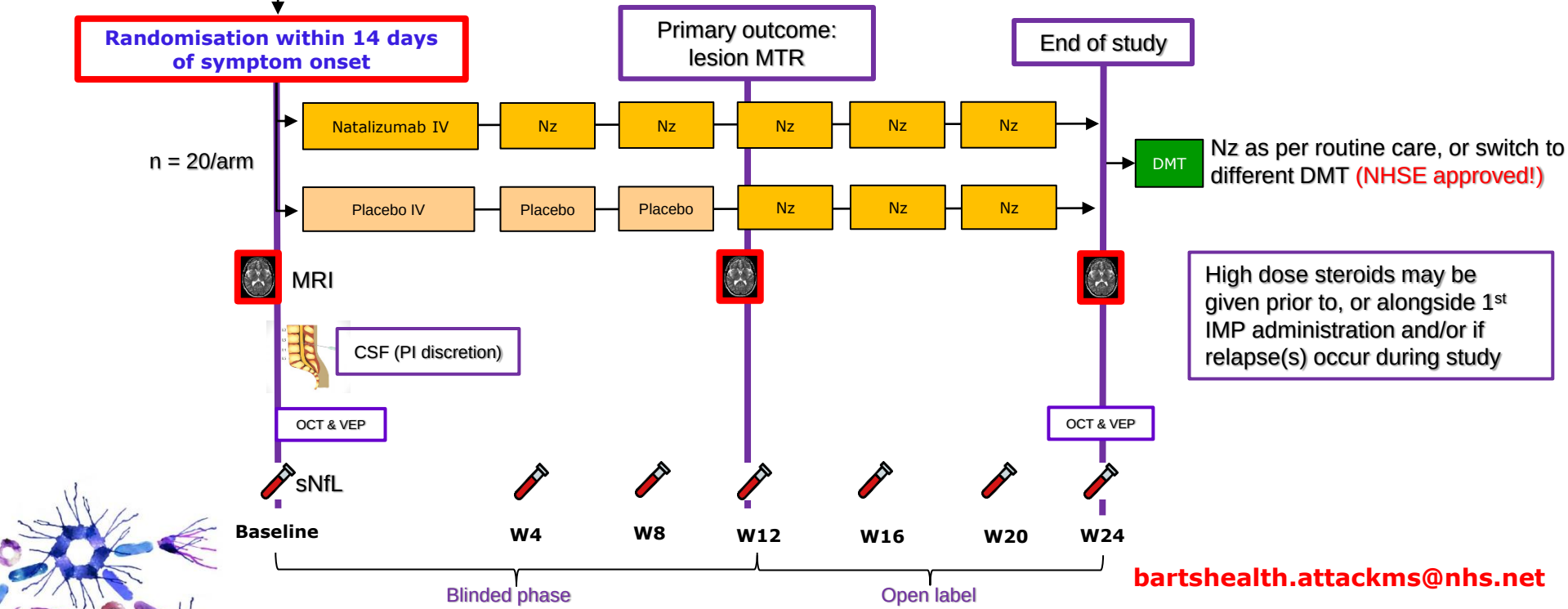
CIS/McDonald MS
(optic neuritis, brainstem, spinal cord, other)

MRI suggestive of demyelination
(at least 2 lesions in typical location)

Randomisation within 14 days of symptom onset

Primary objectives:

- To establish whether it is feasible to enrol people at first manifestation of a clinically isolated syndrome of demyelination (CIS), or McDonald MS, within 14 days
- To test Natalizumab (Tysabri®) 300mg, intravenously over 24 weeks for safety, efficacy, and to advance mechanistic understanding in pwMS.



High dose steroids may be given prior to, or alongside 1st IMP administration and/or if relapse(s) occur during study

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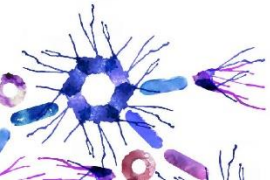
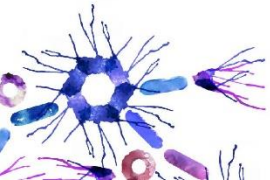
Hypotheses

- FEASIBILITY: Rapid recruitment for very early disease modifying treatment is feasible in the NHS.
- EFFICACY: Natalizumab at disease onset is a safe and effective DMT to prevent myelin and axonal loss from onset in people with clinically isolated syndrome of demyelination/McDonald MS.
- CLINICAL SAFETY: Natalizumab at disease onset is associated with minimal adverse risk.



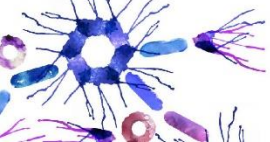
Inclusion criteria

- Patient with CIS or MS at first presentation
- Patients have ≥2 lesions on T_2 weighted MRI suggestive of demyelination
- Male or Female, age 18-45 years

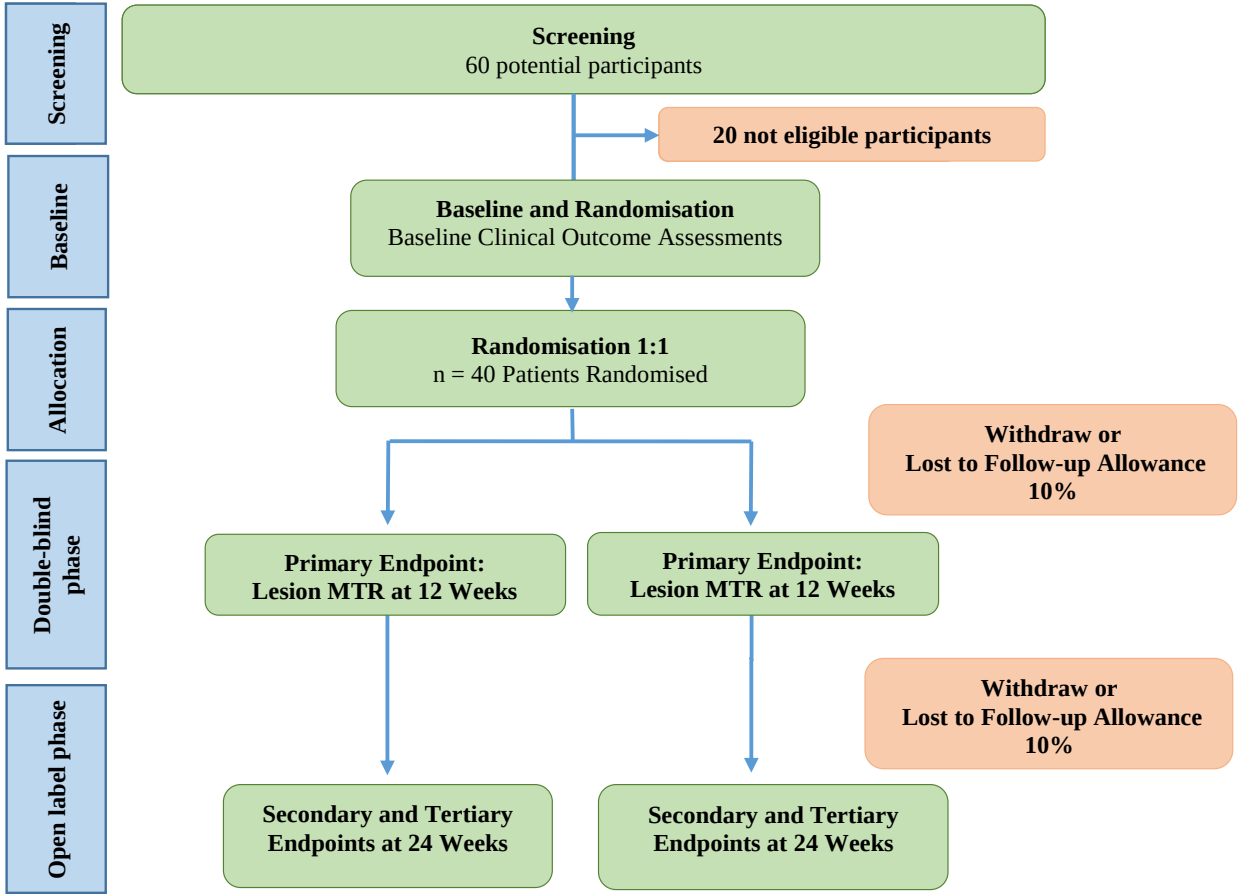


Exclusion criteria

- Hypersensitivity to Natalizumab or incipients.
- Evidence of chronic demyelinating hypo-intensities (“black holes”) on screening MRI.
- Progressive multifocal leukoencephalopathy (PML).
- Patients with increased risk for opportunistic infections, including immunocompromised patients.
- Known active malignancies, except for patients with cutaneous basal cell carcinoma.
- Implants such as pacemaker, aneurysm clip in the brain and MR-incompatible prosthetic heart valves.
- Claustrophobia rendering repeated MRI impossible.



Trial flow chart



Trial schedule I

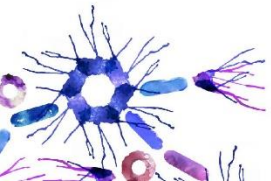
AttackMS: Schedule of Assessments										
Study Procedures	**Visit 1 (Screening Visit)**	**Visit 2 (Baseline and Randomisation Visit)**	**Visit 3**	**Visit 4**	**Visit 5[i]**	**Visit 6**	**Visit 7**	**Visit 8 (End of Trial)**	**Early Withdrawal**	**Unscheduled Visit**
		Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24		
	-14 days	n/a	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days		
		M 0	M 1	M 2	M 3	M 4	M 5	M 6		
Informed Consent Form[a]	X									
Medical History, Drug History, Demographic information & Concomitant Medication[b]	X									
Review of diagnostic brain MRI (optional spinal cord)	X									
Vital signs	X	X	X	X	X	X	X	X	X	
Height and Weight	X							X	X	
Physical Examination[d]	X							X	X	X
Expanded Disability Status Scale (EDSS)	X		X		X			X	X	
Nine-Hole Peg Test (9-HPT)	X		X		X			X	X	
Timed-25 Foot Walk (T25-FW)	X		X		X			X	X	
Symbol Digit Modalities Test (SDMT)	X		X		X			X	X	
Neurological Fatigue Index-MS (NFI-MS) Questionnaire[h]	X		X		X			X	X	
Sloane Low Contrast Visual Acuity Test (SLCVA)	X		X		X			X	X	
Randomisation[c]		X								
Inclusion and Exclusion		X								
Concomitant Medication Review[b]		X	X	X	X	X	X	X	X	

Trial schedule II

Adverse Events Review[E]		X	X	X	X	X	X	X	X	
Study Procedures	**Visit 1 (Screening Visit)**	**Visit 2 (Baseline and Randomisation Visit)**	**Visit 3**	**Visit 4**	**Visit 5[I]**	**Visit 6**	**Visit 7**	**Visit 8 (End of Trial)**	**Early Withdrawal**	**Unscheduled Visit**
		Week 1	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24		
	-14 days	n/a	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days		
		M 0	M 1	M 2	M 3	M 4	M 5	M 6		
Brain MRI (Queen Square)[g]		X			X			X	X	
Visually Evoked Potentials (VEP)[f]		X						X	X	
Optical Coherence Tomography (OCT)[f]		X						X	X	
Lumbar Puncture for Cerebrospinal Fluid (CSF OCB)[i]	X									
Laboratory Assessments										
Biochemistry and Full Blood Count	X									
Urinalysis[k]	X									
Serum Pregnancy Test[j]	X									
Hepatitis B & C, HIV, Syphilis Serology, Thyroid Function Test and Immunoglobulins (M, G, A)		X								
Anti-JCV antibody test		X						X	X	
Serum Neurofilament Light Chain (sNfL)		X	X	X	X	X	X	X	X	
Trial Treatment Administration										
Tysabri® or Placebo		X	X	X						
Tysabri®					X	X	X			

Trial schedule (footnotes)

a	Written Informed Consent Form must be obtained and documented before any trial-specific assessments/procedures take place.
b	Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment.
c	Screening must be completed before randomisation and all assessments, including safety bloods, have been reviewed by the PI or Co- Investigator and are satisfactory. Randomisation must occur within 14 days of participants first symptom. Site should ensure that enough time is given to request the IMP to be sent in order to arrive in time for the participant's visit. The first dose of IMP must be given within 24 hours after randomisation.
d	At screening, perform a complete physical examination that should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at screening should be recorded on the eCRF. During the trial conduct, perform a limited, symptom-directed examination at specified timepoints or as clinically indicated. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.
e	All adverse events will be reported for as long as the participant remains in the trial. The PI should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the PI, the participant is lost to follow up, or the participant withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.
f	OCT and VEP can be completed after first IMP dose within window of +/- 5 days.
g	A brain MRI with contrast is expected to be done at the trial site prior to the study team becoming involved. Findings of this MRI will contribute to evaluating eligibility. If spinal cord MRI is part of the local standard of care, then this may contribute to diagnostic criteria for MS (McDonald MRI criteria, dissemination of lesion[s] in space and time). The research MRI will be obtained, at three time points (baseline, week 12, week 24), at the NMR Research Unit of the UCL Institute of Neurology at Queen Square. Here, MRI brain only will be obtained. If contrast was not given during acquisition of the MRI at the trial site, contrast will be administered as part of the 1st research MRI. MRIs must occur before IMP is administered for each relevant visit.
h	The participant should complete this questionnaire before any other study procedures at required visits.
i	Discussion of treatment after end of trial will take place at this visit.
j	All women of childbearing potential will have a serum pregnancy test at screening.
k	Urinalysis includes dipstick (pH, specific gravity, glucose, protein, ketones, blood), and a microscopic examination if abnormal and applicable will be performed at the site (local laboratory).
l	Lumbar Puncture for CSF OCB may be completed at any point from symptom onset at the PI's discretion.



Partners

ATTACK MS

Queen Mary University of London (Sponsor)

PCTU Pragmatic Clinical Trials Unit

QS MS Queen Square MS Centre

Barts Health NHS Trust

UCL

NHS Chelsea and Westminster Hospital NHS Foundation Trust

Moorfields Eye Hospital NHS Foundation Trust

NHS St George's University Hospitals NHS Foundation Trust

Biogen

Three recruitment sites + one MRI site

Queen Square (MRI)

The Royal London

Chelsea & Westminster

TMG & Committees

Trial Management Group

• Klaus Schmierer	CI, QMUL
• Isabel Monger	QMUL/PCTU
• David Baker	QMUL
• Gavin Giovannoni	QMUL
• Rachel Horne	PPI
• Iman Redha	QMUL
• Lucia Bianchi	QMUL
• Tahera Hussain	QMUL/PCTU
• Richard Hooper	QMUL/PCTU
• Frederik Barkhof	UCL/Queen Square (MRI)
• David MacManus	UCL/Queen Square (MRI)
• Claudia Wheeler-Kingshott	UCL/Queen Square (MRI)
• Marios Yiannakas	UCL/Queen Square (MRI)
• Abir Sanyal	Barts Health/Neurophysiology
• Konstantinos Balaskas	Moorfields Eye Hospital
• Liqun Zhang	PI, St George's Hospital
• Victoria Singh-Curry	PI, Chelsea & Westminster Hospital

Trial Steering Committee

• Jeremy Hobart	Neurologist, Plymouth (Chair)
• Klaus Schmierer	CI, QMUL
• Marie-Claire Good	JRMO
• John Miers	PPI
• Penny Gowland	MR Physicist, Nottingham
• Jennifer Nicholas	Statistician, London School of Hygiene & Tropical Medicine

Data Monitoring Committee (TBC)

• Neil Robertson	Neurologist, Cardiff (Chair)
• Victoria Williams	Neurologist, KCL/Guy's & St Thomas's
• Gary Cutter	Statistician, Birmingham, Alabama (USA)

PPI

Rachel Horne
@RachelHorne19

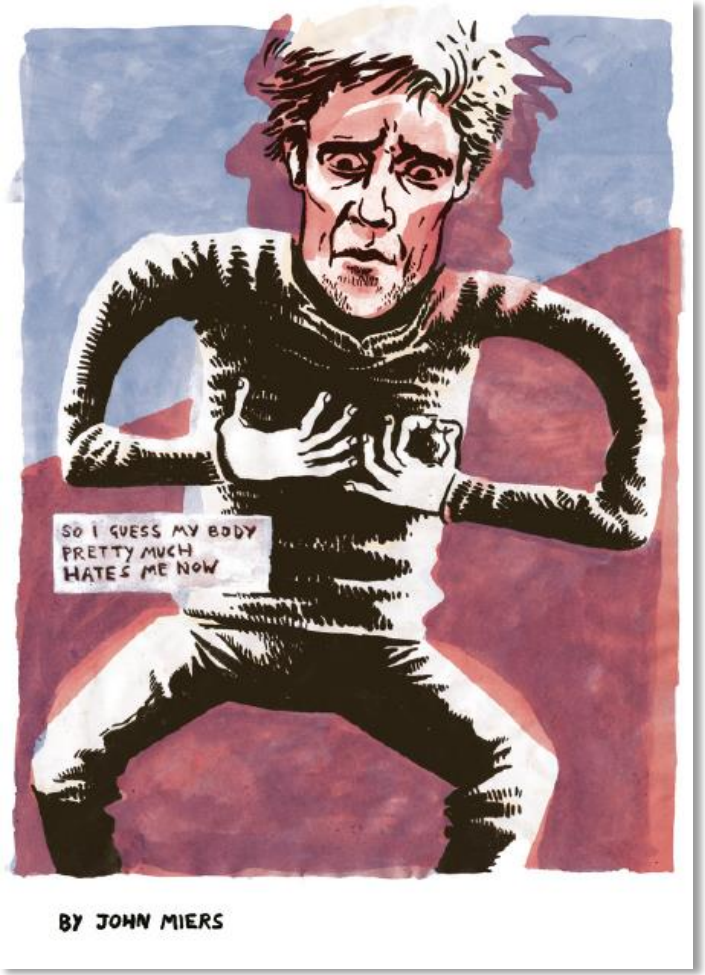
Excited about #AttackMS study launching in December
Study aimed at ppl presenting at A&E with early signs of MS. If agree they will have MRI, tests etc and will start on Tysabri in 14 days if MS confirmed.
Study aims to see if v early use of v effective DMT slows MS.
Need ur help..

2:34 PM · Jun 30, 2022 · Twitter Web App

20 Retweets **5** Quote Tweets **86** Likes

https://twitter.com/RachelHorne19/status/1542501824137072647

PPI



https://johnmiers.com/

Daily Mail

Giving powerful drugs to patients who have suspected multiple sclerosis could spare them lifetime of debilitating symptoms, experts believe

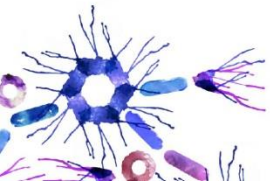
- **People with multiple sclerosis (MS) face a worsening symptoms as years go by**
- **The debilitating conditions leads to mobility, muscle, bladder and eye problems**
- **Experts believe people who have not been formally diagnosed could be treated**
- **A new drug is being tested on those in the early stages of the incurable condition**

By JO MACFARLANE FOR THE MAIL ON SUNDAY
PUBLISHED: 23:08, 6 August 2022 | **UPDATED:** 14:48, 7 August 2022

Giving powerful medication to patients suspected of having multiple sclerosis – but who are not yet formally diagnosed – could spare them a lifetime of debilitating symptoms, experts believe.

At present, the most potent drug treatments that tackle the underlying causes of the neurological disease are reserved for those with more advanced cases.

But a growing body of research suggests giving these types of medicines before symptoms worsen could keep the condition stable for at least a decade.



ATTACK MS

Natalizumab for the treatment of people with inflammatory demyelination suggestive of multiple sclerosis, or definite multiple sclerosis, at first presentation

LOOKING FOR RESEARCH PARTICIPANTS!

- **Patient with stroke-like syndrome, but doesn't HAVE a stroke?**
- **Symptom onset <14 days ago?**
- **Age 18-45 years?**
- **MRI suggestive of demyelination?**

Please contact the AttackMS team via:

Study Doctor: Professor Klaus Schmierer *or* **Study Coordinator:** Kimberley Allen-Philbey

Email: bartshealth.attackms@nhs.net

Telephone: 07512 561375 or 020 7377 7000 (ask for on-call neurologist)

AttackMS Poster version 0.1 29Nov2021
IRAS number: 1003822