

New Therapies in the Management of Multiple Sclerosis

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Disclosures

- ▶ Researcher
 - ▶ Atara Biotherapeutics, Sanofi, Genentech, Jazz Pharma, BMS, Kyverna
- ▶ Consultant
 - ▶ Atara Biotherapeutics
- ▶ Speaker
 - ▶ Sanofi, Serono
- ▶ Advisor
 - ▶ TG Therapeutics, Genentech



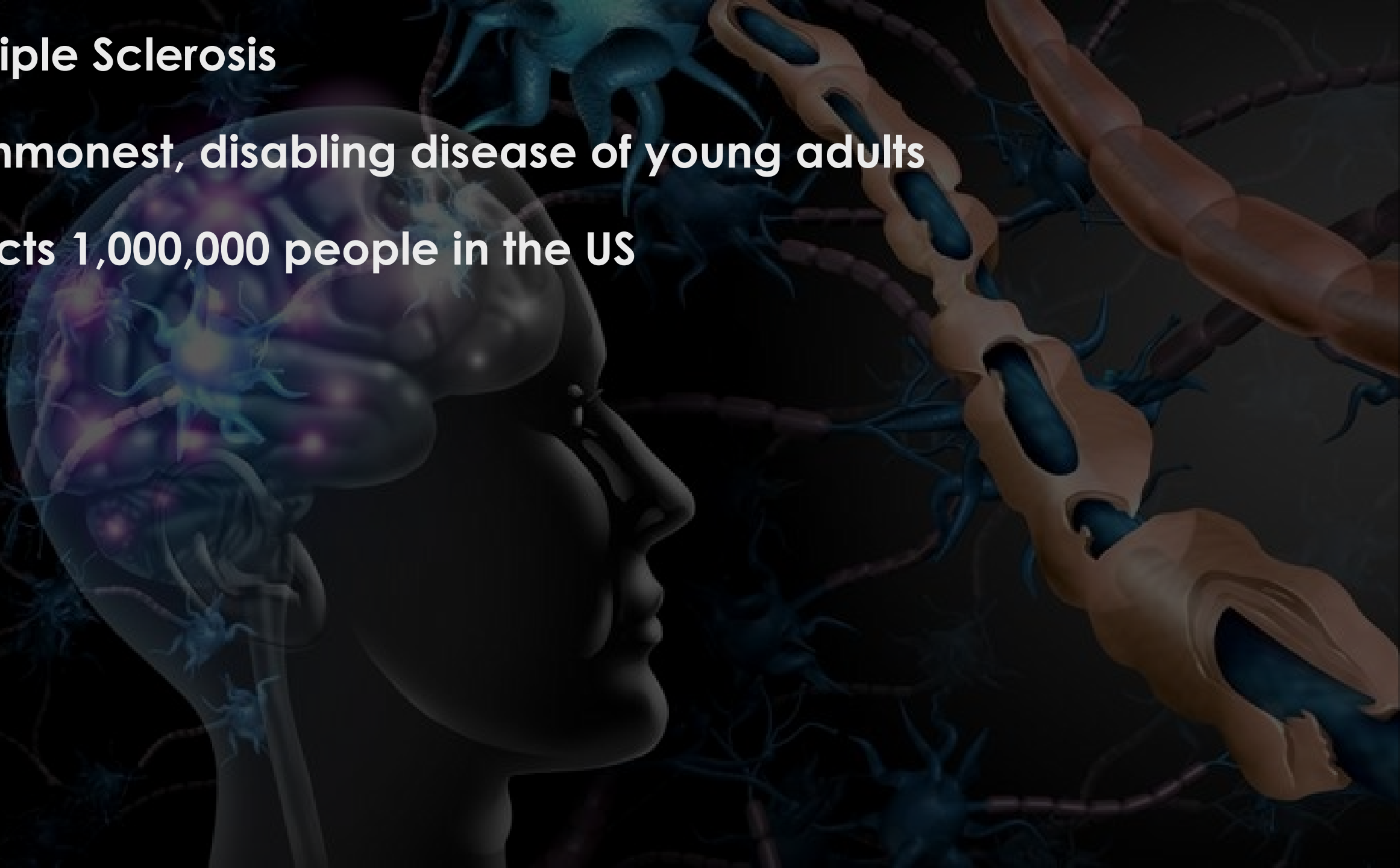
Outline

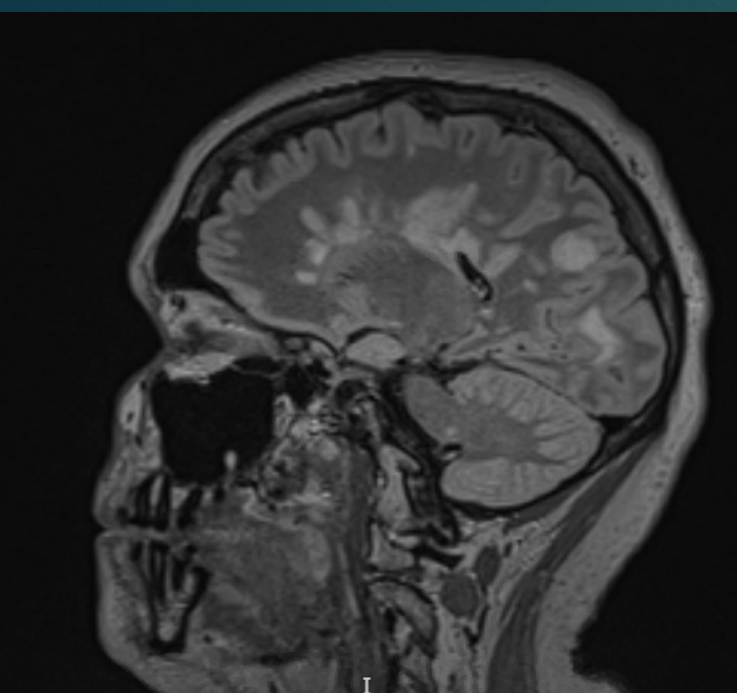
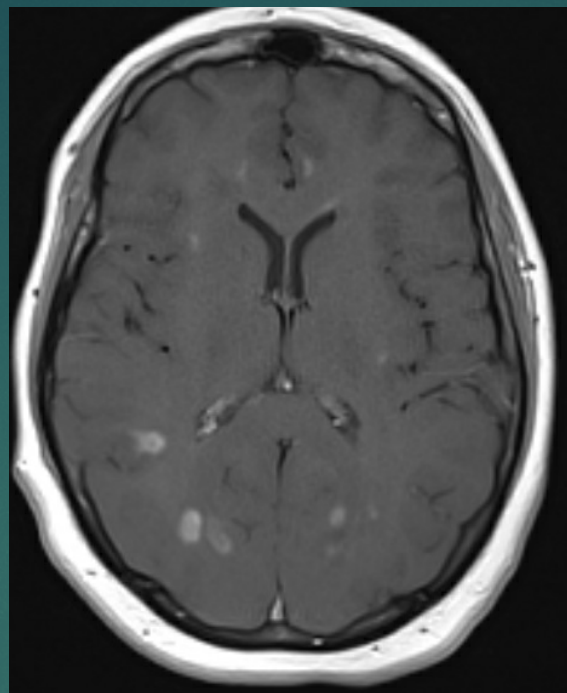
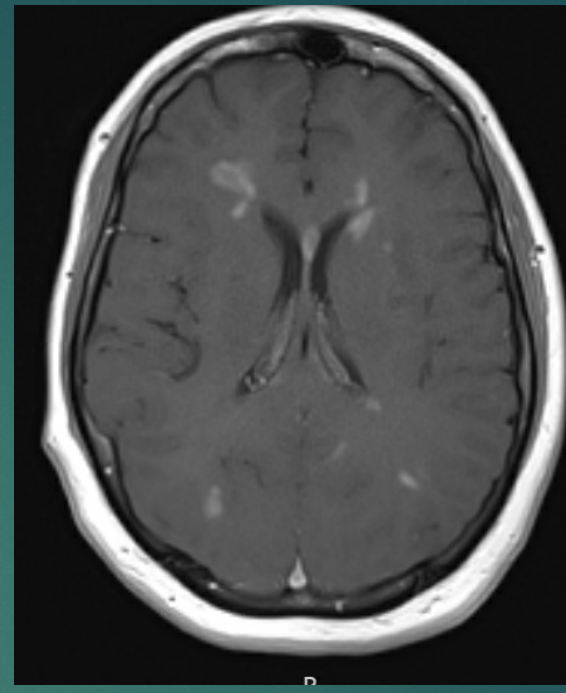
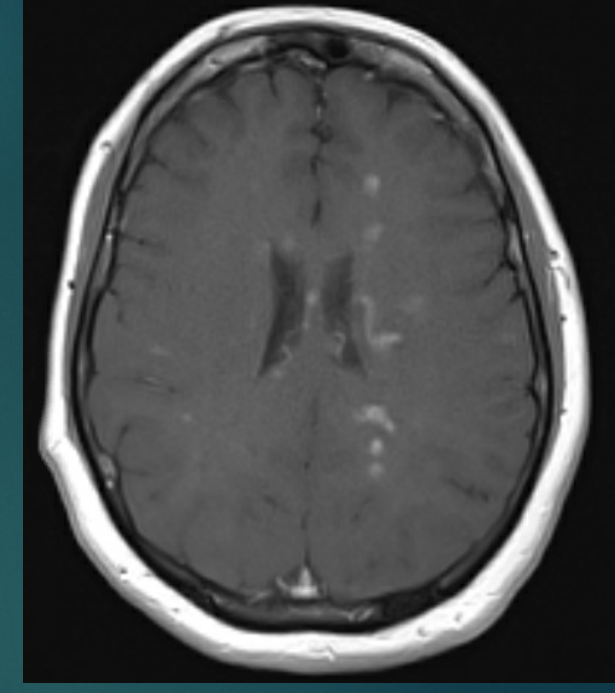
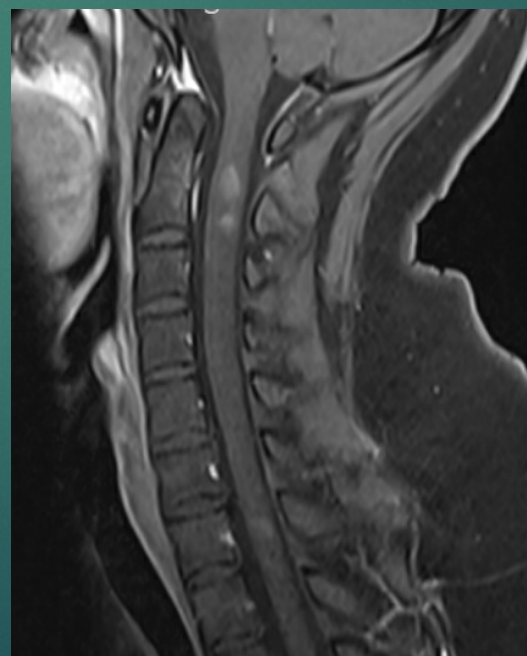
- ▶ Brief MS Background
- ▶ MS Treatment Landscape
- ▶ New DMTs in 2024
- ▶ MS Research Landscape

Multiple Sclerosis

Commonest, disabling disease of young adults

Affects 1,000,000 people in the US



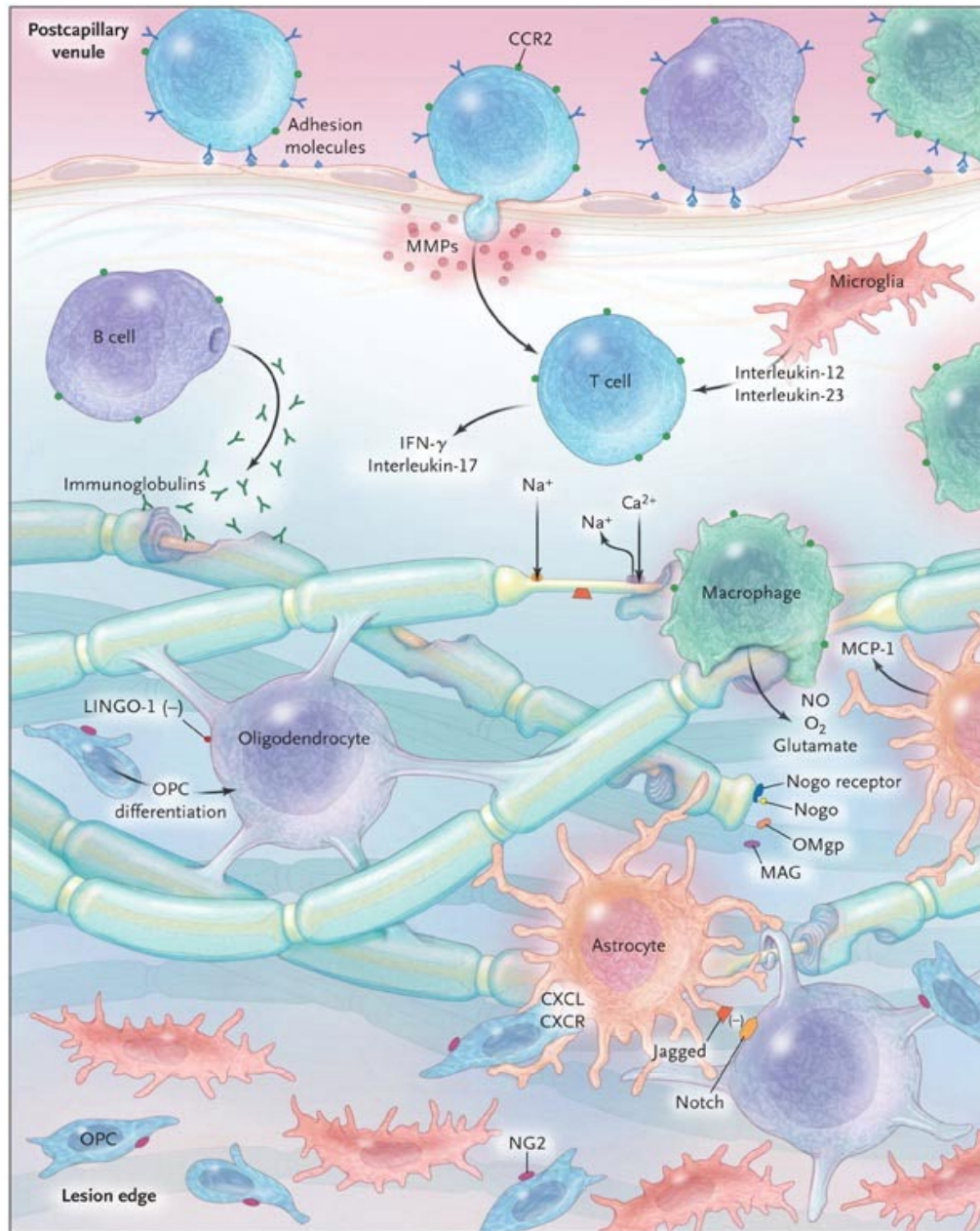


- ▶ Prevalence
 - ▶ Highly variable worldwide
 - ▶ 3:1 Female : Male ratio
 - ▶ Age of Onset: Usually starts in 30s but onset can range from age 5 to 65

MS Epidemiology

- ▶ Geographic latitude
- ▶ Vitamin D deficiency
- ▶ EBV / History of mononucleosis
- ▶ Tobacco use
- ▶ Adolescent obesity
- ▶ Family History

MS Risk Factors



Inflammation in the Brain in MS

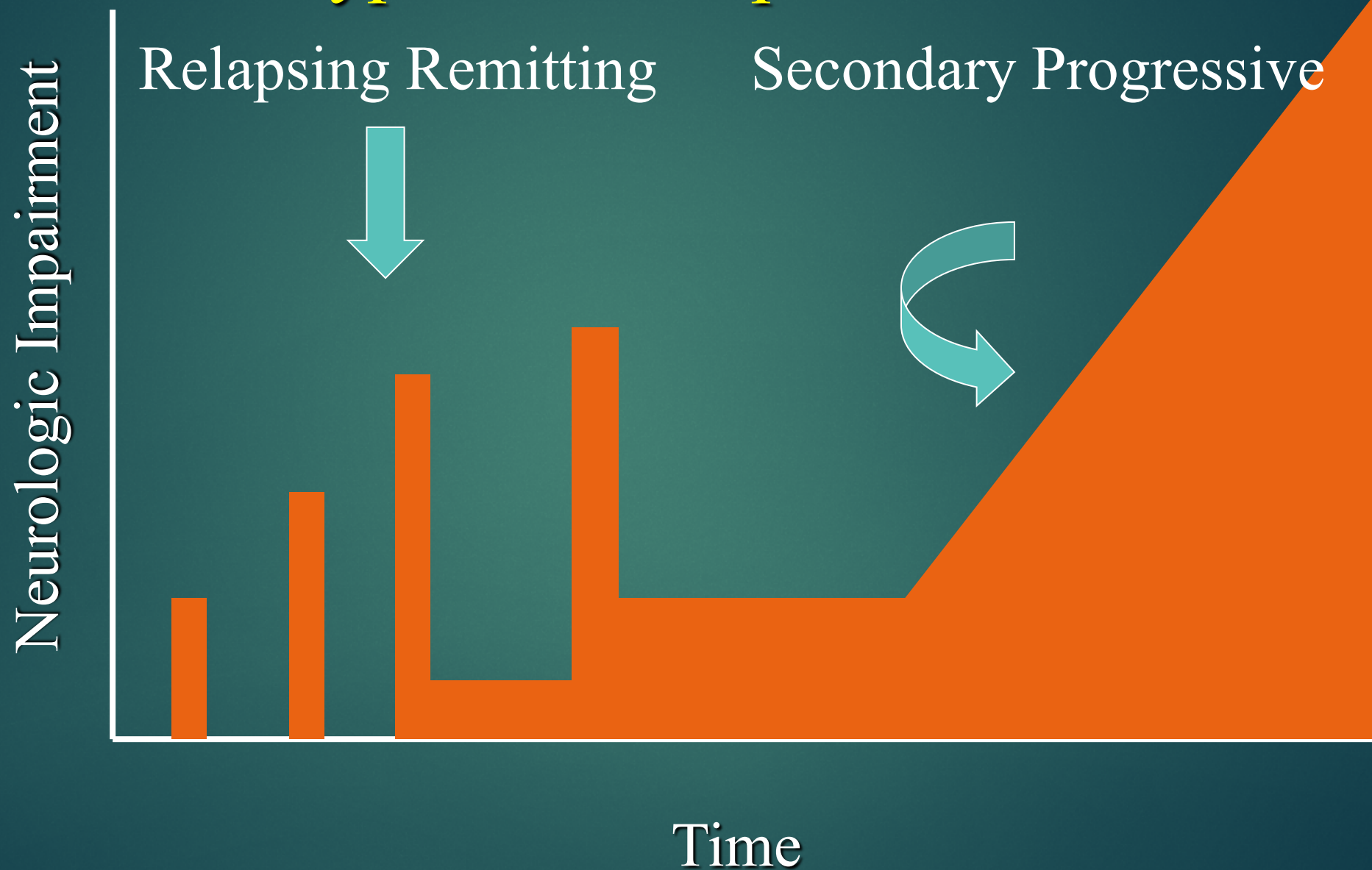
Cells: T cells , B cells , Microglia

Antibodies

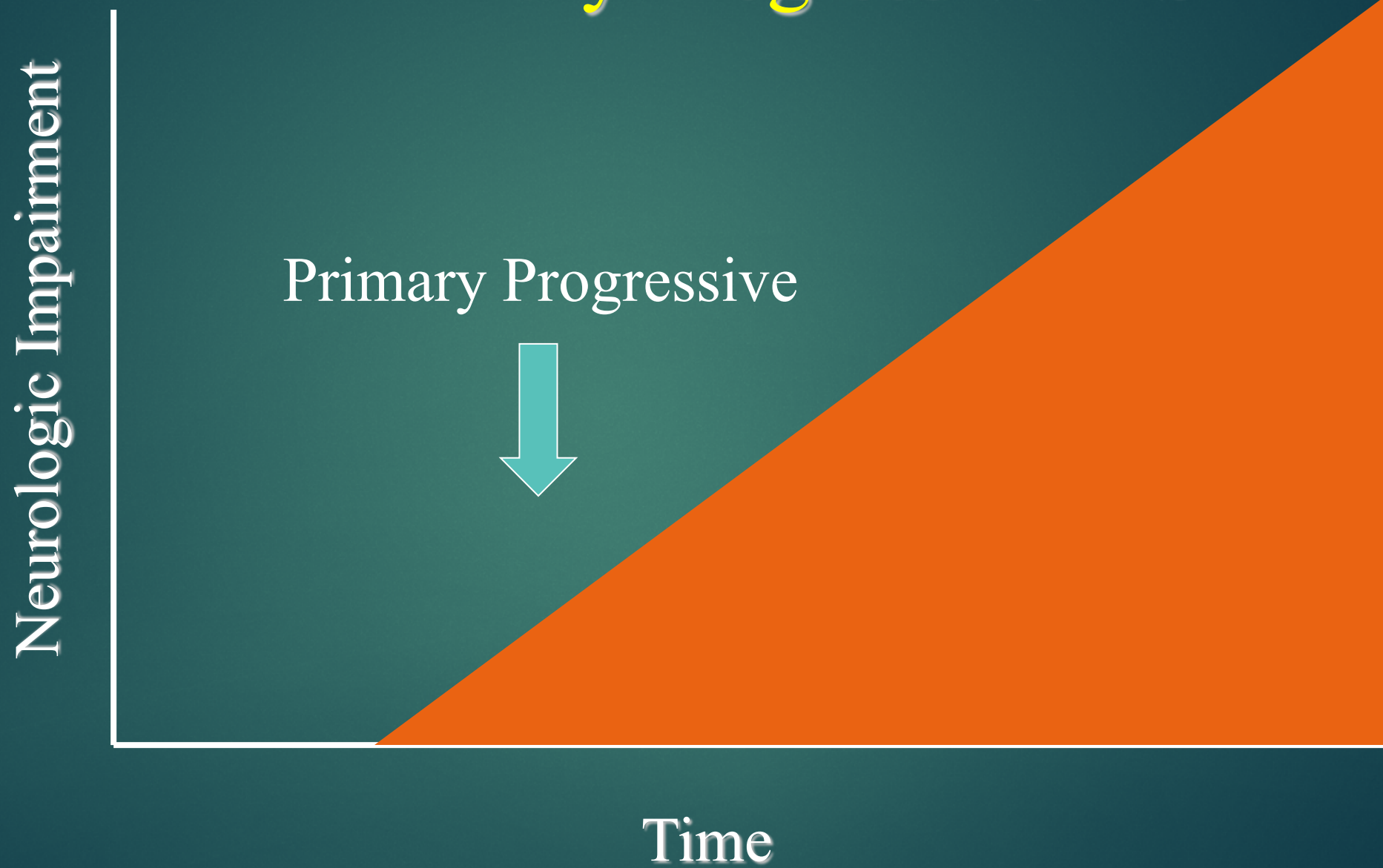
Compartmentalized

Smoldering inflammation

Types of Multiple Sclerosis

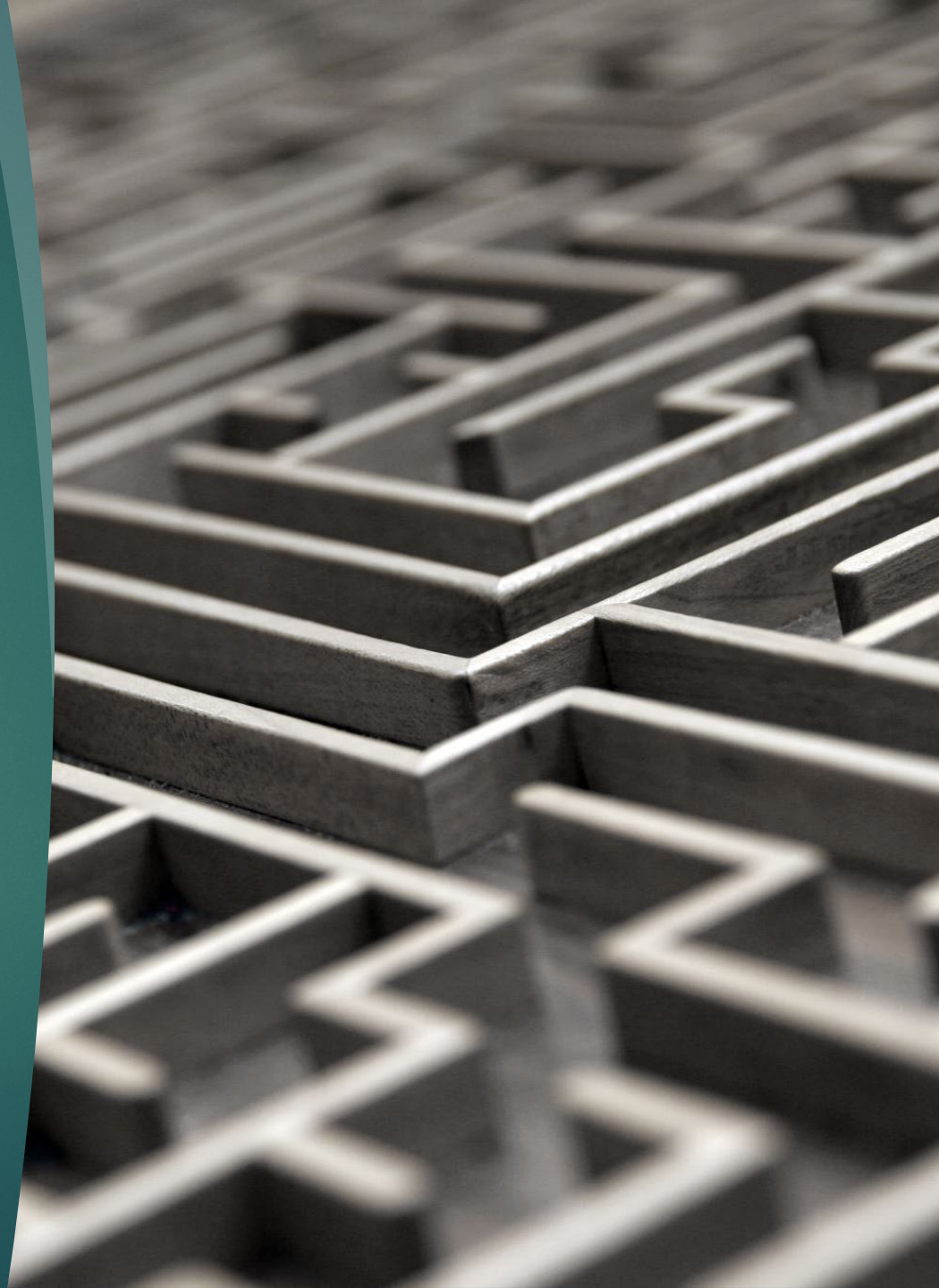


Primary Progressive MS



Approach to DMT Decisions

- ▶ There are many DMT options available in past 7 years
- ▶ Patients and providers may have different goals
- ▶ Shared-decision making is essential
- ▶ Dedicated treatment visit is useful
- ▶ Considerations include:
 - ▶ Effectiveness
 - ▶ Safety
 - ▶ Tolerability
 - ▶ Individual Risk Tolerance
 - ▶ Convenience
 - ▶ Cost



MS: Disease Modifying Therapies (DMT)

1993-2018

- interferon beta-1b (Betaseron)-1993
- interferon beta-1a (Avonex) --1996
- glatiramer acetate (Copaxone)—1996
- mitoxantrone (Novantrone)--2000
- interferon beta-1a (Rebif)—2002
- natalizumab (Tysabri)—2006
- fingolimod (Gilenya)—2010
- teriflunomide (Aubagio)—2012
- dimethyl fumarate (Tecfidera)--2013
- peginterferon beta-1a (Plegridy)—2014
- alemtuzumab (Lemtrada)—2014
- ocrelizumab (Ocrevus)—2017

2019-2024

- siponimod (Mayzent) 2019
- cladribine (Mavenclad) 2019
- diroximel fumarate (Vumerity)--2019
- monomethyl fumarate (Bafiertam)—2020
- ozanimod (Zeposia)—2020
- ofatumumab (Kesimpta)—2020
- ponesimod (Ponvory)—2021
- ublituximab (Briumvi) – 2022
- natalizumab-sztn (Tyruko) --2023

siponimod (Mayzent) - 2019

MOA	S1P 1&5 selective modulator, blocks lymphocytes egress from LN
ARR	55% reduction in ARR v placebo
Disability	21% RR reduction in time to 3mCDP v placebo
MRI	81% RR in number of new or enlarging T2 lesions
Route, Frequency	Daily, po, starter pack for most
Safety	Infections, Crypto, VZV, PML, macular edema, bradyarrhythmia, PRES, cutaneous malignancies
Side effects	HA, HTN
Other	Discontinuation syndrome Eye exam if hx of DM or uveitis Skin checks

cladribine (Mavenclad) - 2019

MOA	Selective depletion of T and B lymphocytes;
ARR	58% RR reduction in ARR v placebo
Disability	33% reduction in 3mCDP v placebo
MRI	73% reduction in new T2 lesions v placebo
Route, Frequency	8-10 days of oral medication per year for 2 years; weight based
Safety	Malignancy in clinical trial (no malig in placebo group; lymphopenia, VZV, teratogenic
Side effects	Headache, lymphopenia

diroximel fumarate (Vumerity) - 2019

MOA	NRF2 activator, anti-oxidant effect Prodrug of monomethyl fumarate
ARR	Based on bioavailability studies with dimethyl fumarate
Disability	Based on bioavailability studies with dimethyl fumarate
MRI	Based on bioavailability studies with dimethyl fumarate
Route, Frequency	po, BID
Safety	PML, VZV, angioedema, lymphopenia
Side effects	Flushing, GI effects, indigestion

monomethyl fumarate (Bafiertam) -2020

MOA	NRF2 activator, anti-oxidant effect
ARR, disability, MRI	Based on bioequivalence studies with dimethyl fumarate
Route, Frequency	po, BID
Safety	PML, VZV, angioedema, lymphopenia
Side effects	Flushing, GI effects, indigestion

ozanimod (Zeposia) - 2020

MOA	S1P 1&5 modulator, blocks lymphocytes egress from LN
ARR	48% reduction in ARR v Avonex
Disability	No sig difference in 3m CDP between groups
MRI	63% reduction in mean t1Gd+ lesions v Avonex
Route, Frequency	Daily, po, 7-day titration
Safety	Infection, HSV, VZV, crypto, PML, HTN, cutaneous malignancy, macular edema, fetal risk
Side effects	HTN
Other	Discontinuation syndrome

ofatumumab (Kesimpta) - 2020

MOA	Anti-CD20, B-cell depletion
ARR	58% ARR reduction v. Aubagio
Disability	34% reduction in 3mCDP v Aubagio
MRI	98% reduction of mean # new gd+ T1 lesions
Route, Frequency	Monthly, sq
Safety	Rare serious infections (2%)
Side effects	ISR (10%),
Other	Weekly titration x 3 weeks; check Hep B

ponesimod (Ponvory) - 2021

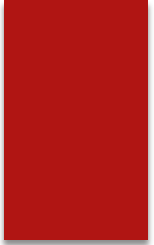
MOA	S1P1 receptor 1 & 5 modulator; blocks lymphocytes egress from LN
ARR	30% reduction in ARR v Aubagio
Disability	no difference v Aubagio in time to 3mCDP
MRI	59% reduction in new T1Gd+ lesions v Aubagio
Route, Frequency	Daily, po
Safety	Infection, HSV, VZV, crypto, PML, HTN, cutaneous malignancy, macular edema, fetal risk
Side effects	HTN, increased LFT
Other	Contraindicated in patients 2 nd or 3 rd degree AV block; or hx MI, angina , stroke or TIA Discontinuation syndromes

ublituximab (Briumvi) - 2022

MOA	anti-CD20, glycoengineered, B-cell depleting
ARR	59% reduction in ARR v Aubagio
Disability	Lower CDP at 12 weeks but no sig
MRI	97% reduction in T1Gd+ lesions v Aubagio
Route, Frequency	IV, q 6 mo, 1 hour infusion
Safety	Infusion reactions -48%, 3 deaths – post measles encephalitis, pneumonia and salpingitis after ectopic
Side effects	Infusion reactions
Other	First dose of 150mg, then 450mg IV dose 2 weeks later;

natalizumab –sztn (Tyruko) - 2023

MOA	Binds α 4-integrin, inhibiting migration of immune cells across BBB
ARR , Disability, ARR	Extrapolated approval based on bio similarity with Tysabri
Route, Frequency	IV, monthly
Safety	PML
Side effects	
other	First biosimilar in RRMS

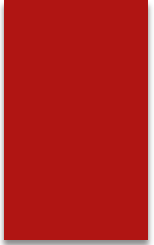


IFN	GA	Pyrimidine Synthesis Inhibitor	S1P modulator (anti- trafficking)	α 4-integrin inhibitor (anti- trafficking)	Fumarate (nrf-1 activator)	Anti-CD20 (Anti B cell)	Immune Reconstitution
Avonex Betaseron Extavia Plegridy Rebif	Copaxon e Glatopa	Aubagio	Gilenya Mayzent Ponvory Zeposia	Tysabri Tyruko	Tecfidera Vumerity Bafiertam	Ocrevus Rituxan Kesimpta Briumvi	Mavenclad Lemtrada

DMT by Mechanism of Action

Injectable	Oral	Intravenous Infusion
Avonex Betaseron Copaxone Extavia Glatopa Kesimpta Plegridy Rebif	Aubagio Bafiertam Gilenya Mavenclad Mayzent Ponvory Tecfidera Vumerity Zeposia	Briumvi Lemtrada Novantrone Ocrevus Tysabri Tyruko Rituxan

DMT by Route of Administration



Platform Therapies	Moderate Efficacy	High-efficacy
Avonex Betaseron Copaxone Extavia Glatopa Plegridy Rebif	Aubagio Bafiertam Gilenya Mayzent Ponvory Tecfidera Vumerity Zeposia	Mavenclad Briumvi Lemtrada Ocrevus Tysabri Tyruko Rituxan Kesimpta Lemtrada

DMT by Efficacy

Lowest risk	↔	↔	Highest-Risk
Copaxone Glatopa Avonex Betaseron Plegridy Rebif Extavia	Aubagio	Mavenclad Briumvi Ocrevus Tysabri Tyruko Rituxan Kesimpta Bafiertam Gilenya Mayzent Ponvory Tecfidera Vumerity Zeposia	Lemtrada Novantrone

DMT by Risk



- ▶ Principals of DMT Decisions
 - ▶ Treat early
 - ▶ High-efficacy DMT early more likely to prevent disability later **on average**
 - ▶ **Individualize** treatment decisions
- ▶ Considerations include:
 - ▶ Effectiveness
 - ▶ Safety / Risk
 - ▶ Individual Risk Tolerance of patient
 - ▶ Tolerability
 - ▶ Convenience
 - ▶ Cost

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New DMTs in 2024?

- ▶ Tolebrutinib
 - ▶ BTKi – Bruton's Tyrosine Kinase inhibitor
 - ▶ Oral, CNS penetrant
 - ▶ Inhibits BTK expressed in microglia and B cells
 - ▶ Microglia drive CNS inflammation in MS
 - ▶ Phase-2 study in RMS
 - ▶ Novel design using MRI data as primary outcome
 - ▶ At 12 weeks, there was a significant dose-dependent reduction in number of new Gd+T1 lesions; well tolerated and safe
 - ▶ Now in phase 3 trials for RRMS, SPMS, PPMS
 - ▶ Data from phase 3 trials expected this summer;

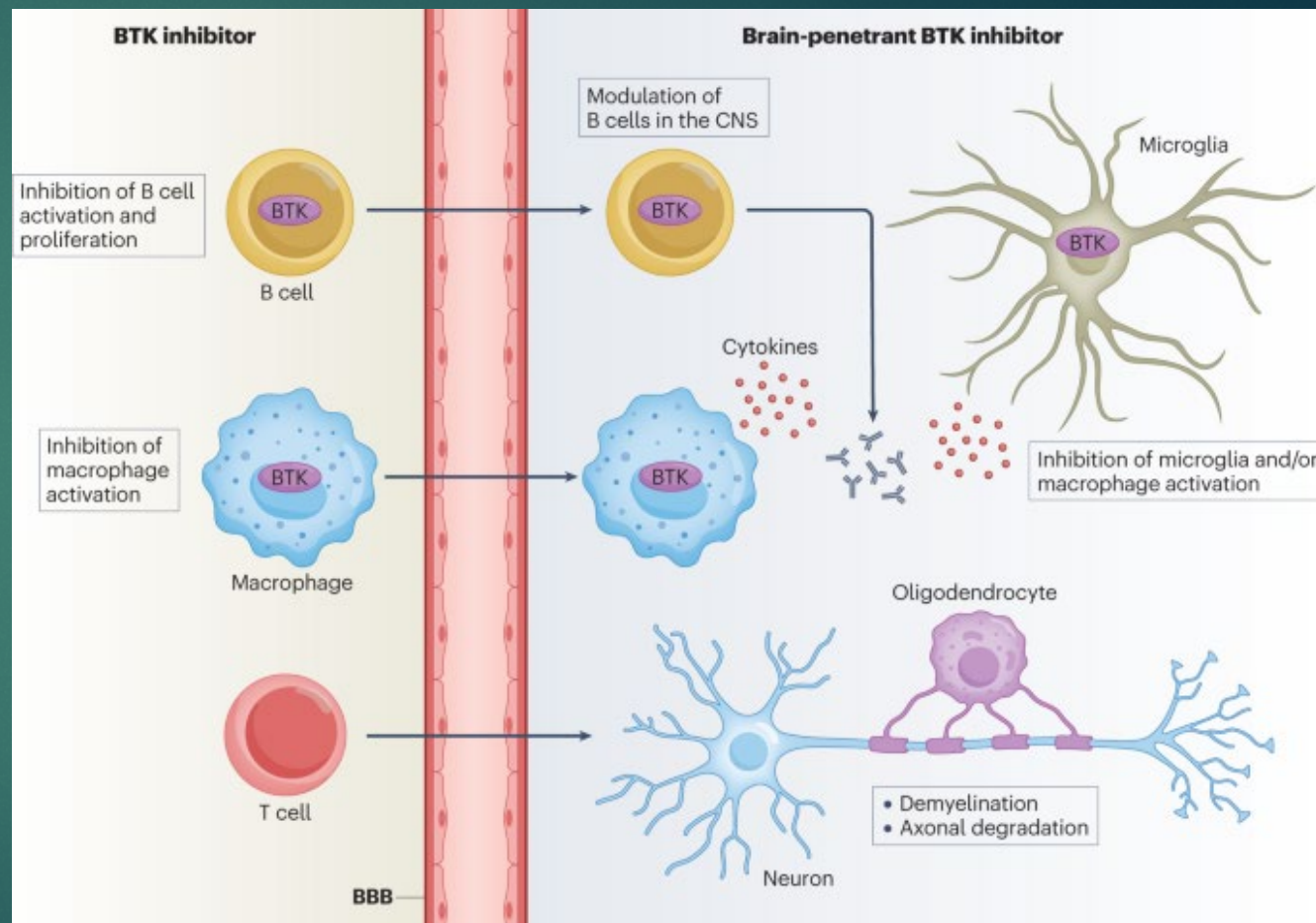


MS Research Landscape

- ▶ Immunotherapy
- ▶ Repair / Remyelination
- ▶ Cure

Immunotherapy: BTKi

- ▶ Multiple BTKi in phase 3 trials for ALL forms of MS
- ▶ Tolebrutinib
- ▶ Fenobrutinib
- ▶ Remibrutinib
- ▶ Masitinib
- ▶ **Evobrutinib trials in RRMS failed – December 2023**



Immunotherapy: Frexalimab

- ▶ Phase 2 study
 - ▶ 89% reduction in new enhancing MRI lesions at 12 weeks
 - ▶ Relapsing-remitting MS
 - ▶ Monthly infusions
 - ▶ Well tolerated
 - ▶ **New mechanism of action** – blocks CD40/CD40L pathway which impairs immune cell function without depleting them
 - ▶ Studies in relapsing and progressive MS underway

Immunotherapy: ANK700

- ▶ In phase 1 trials – MoveS-it
- ▶ Concept of “inverse vaccine”
- ▶ Reintroduce the “friendly self protein” to encourage immune system to ignore it instead of attack
- ▶ A myelin protein is part of ANK700



Repair / Remyelination

- ▶ Clemastine – ReBuild Trial
- ▶ May 2023 paper in PNAS
- ▶ Stimulates the differentiation of myelin producing cells
- ▶ Sedating, anti-histamine

PNAS

RESEARCH ARTICLE

NEUROSCIENCE

 OPEN ACCESS

MWF of the corpus callosum is a robust measure of remyelination: Results from the ReBUILD trial

Eduardo Caverzasi^{a,b,1} , Nico Papinutto^{a,1} , Christian Cordano^{a,1} , Gina Kirkish^a, Tristan J. Gundel^a, Alyssa Zhu^a, Amit Vijay Akula^a, W. John Boscardin^{c,d}, Heiko Neeb^{e,f} , Roland G. Henry^a, Jonah R. Chan^a , and Ari J. Green^{a,g,2}

Edited by Lawrence Steinman, Stanford University, Stanford, CA; received October 17, 2022; accepted March 13, 2023

Myelin repair is an unrealized therapeutic goal in the treatment of multiple sclerosis (MS). Uncertainty remains about the optimal techniques for assessing therapeutic efficacy and imaging biomarkers are required to measure and corroborate myelin restoration. We analyzed myelin water fraction imaging from ReBUILD, a double-blind, randomized placebo-controlled (delayed treatment) remyelination trial, that showed a significant reduction in VEP latency in patients with MS. We focused on brain regions rich in myelin. Fifty MS subjects in two arms underwent 3T MRI at baseline and months 3 and 5. Half of the cohort was randomly assigned to receive treatment from baseline through 3 mo, whereas the other half received treatment from 3 mo to 5 mo post-baseline. We computed myelin water fraction changes occurring in normal-appearing white matter of corpus callosum, optic radiations, and corticospinal tracts. An increase in myelin water fraction was documented in the

Significance

Putative imaging biomarkers of myelin in MS have been correlated with pathological evidence of myelin loss in the context of a complex pathological environment. However, they have not been shown to improve dynamically with myelin repair because of limited therapeutic

Repair / Remyelination

OCTOPUS Trial (UK) and **PLATYPUS Trial** (Australia)

Progressive MS – primary and secondary

Multi-arm, multi-state (MAMS) trial design

Testing multiple drugs at once

Patient randomized to one of three groups:

Metformin or **Lipoic Acid** or **Placebo**

Metformin has been shown to have remyelinating potential in MS

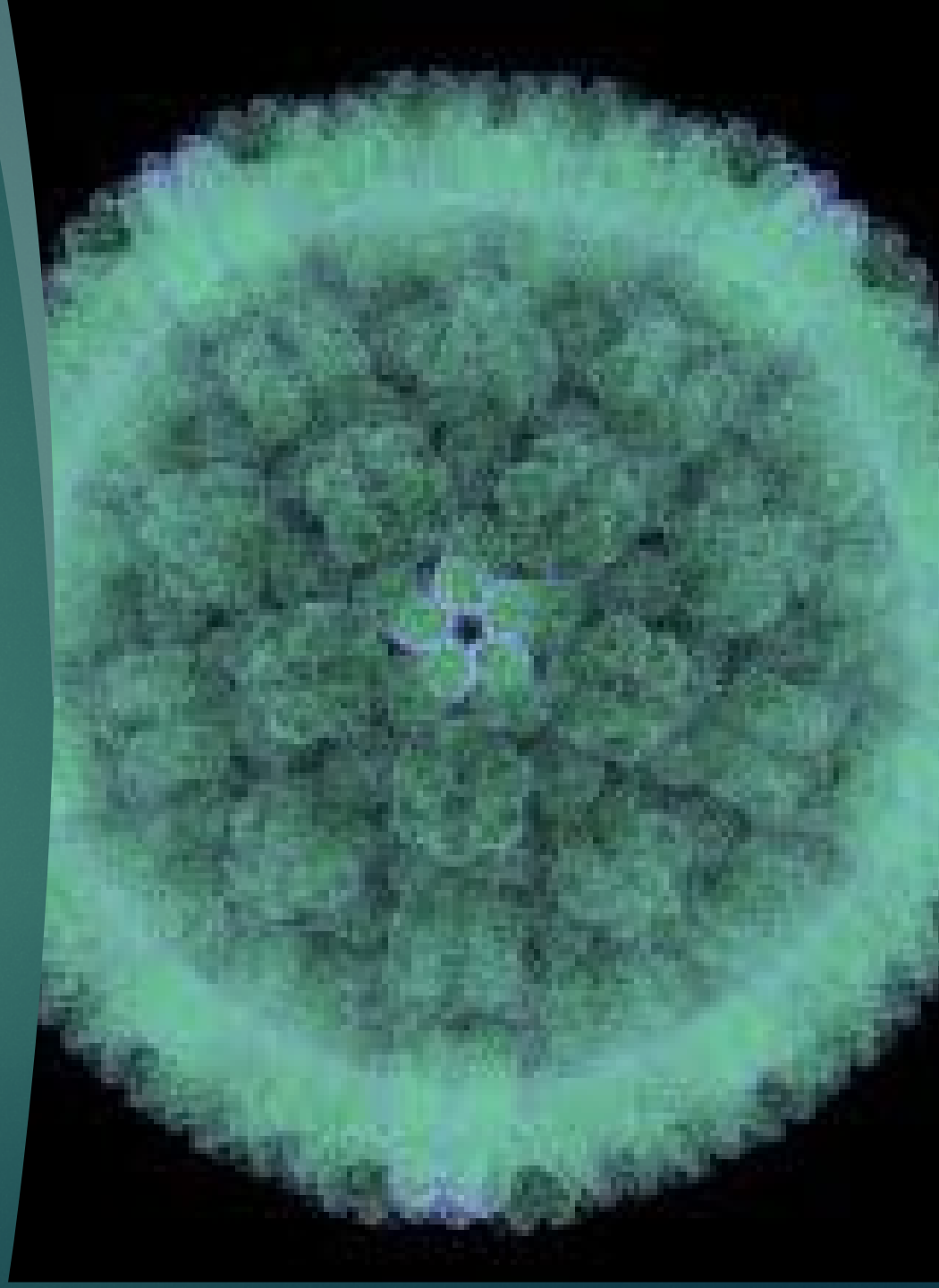
Lipoic Acid has been shown to be neuroprotective in MS in phase 2





Epstein-barr virus

- ▶ Human herpes virus 4
- ▶ Ancient virus that has co-evolved with hosts over the past 100 million years
- ▶ Infects 97% of all humans
- ▶ Causes mononucleosis
- ▶ Establishes lifelong latency and intermittent reactivation after primary infection
- ▶ **EBV virus infects B-cells** and clones them
- ▶ In healthy EBV carriers, infected B cells and controlled by the immune system
- ▶ **In EBV carriers with MS, infected B-cells escape control**



Prospective study in the department of defense using stored blood samples

810 MS patients who developed MS after they enrolled in DOD and 1577 matched controls

EBV seroconversion (going from EBV negative to EBV positive) associated with a 32 fold higher risk of developing MS

RESEARCH

REPORT

MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik^{1,†}, Marianna Cortese^{1,†}, Brian C. Healy^{2,3,4}, Jens Kuhle⁵, Michael J. Mina^{6,7,8}, Yumei Leng⁶, Stephen J. Elledge⁶, David W. Niebuhr⁹, Ann I. Scher⁹, Cassandra L. Munger^{1,†}, Alberto Ascherio^{1,10,11,*}

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. The demyelination in the brain and spinal cord is an immune-mediated process (1) possibly triggered by a

relatively rare disease, has until now impeded such an investigation. Over the course of a 20-year collaboration with the US military, we have identified cases of MS in a cohort composed of active-duty US military personnel between 1993 and 2013, a racially

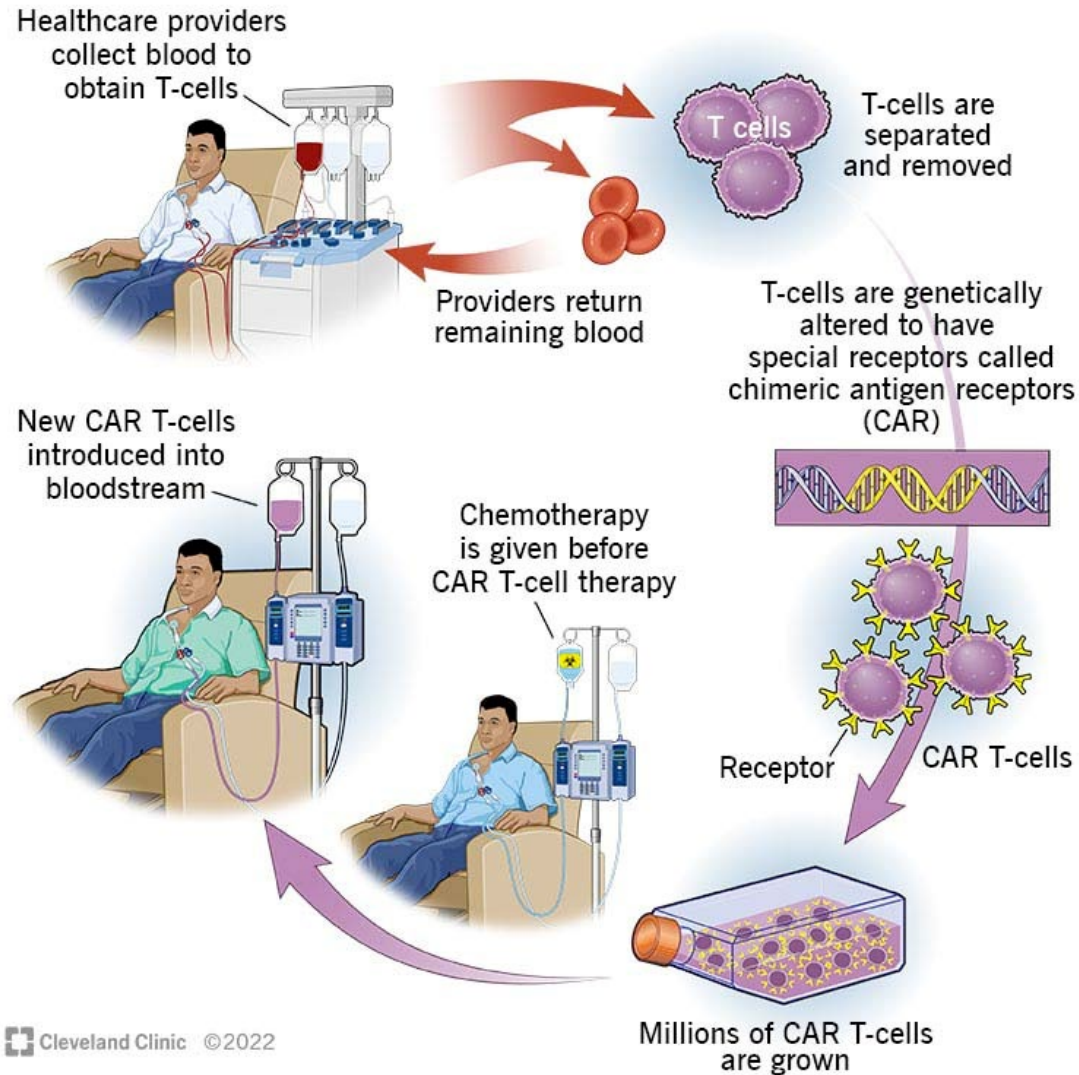
race/ethnicity, dates of collection on active military duty, and dates of diagnosis (Fig. 1A). 801 MS cases were available to assess the association of the individual's age at the time of diagnosis (Fig. 1B), and the time from symptom onset to first sample collection (Fig. 1C).

Only one of 107 controls was an individual who seroconverted to EBV within the last sample, within 1 year before diagnosis. For MS compared with controls, the odds ratio for MS compared with EBV-negative = 26.3 (95% CI = 3.7 to 191.6; *P* = 0.0004 [logistic regression]). Among 107 controls who were EBV-negative, these 35 EBV-converted with EBV seroconverted. The median time from sample to MS diagnosis was 10 years), and matched EBV seroconversion midpoint between sample and the first onset was 7.5

- ▶ EBV infects B cells
- ▶ B cells are fundamental to MS pathophysiology
- ▶ MS develops in those who cannot manage the common infection
- ▶ New clinical trials for MS that target EBV include:
 - ▶ Anti-viral medication
 - ▶ EBV vaccines

Key Take Aways

How CAR T-cell therapy is used to treat cancer



CAR-T cell



Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

Andreas Mackensen^{1,2,8}, Fabian Müller^{1,2,8}, Dimitrios Mougiakakos^{1,2,3,8}, Sebastian Böltz^{2,4}, Artur Wilhelm^{2,4}, Michael Aigner^{1,2}, Simon Völkl^{1,2}, David Simon^{2,4}, Arnd Kleyer^{2,4}, Luis Munoz^{2,4}, Sascha Kretschmann^{1,2}, Soraya Kharboul^{1,2}, Regina Gary^{1,2}, Hannah Reimann^{1,2}, Wolf Rösler^{1,2}, Stefan Uderhardt^{2,4}, Holger Bang⁵, Martin Herrmann^{2,4}, Arif Bülent Ekici⁶, Christian Buettner⁶, Katharina Marie Habenicht⁷, Thomas H. Winkler⁷, Gerhard Krönke^{2,4,8} and Georg Schett^{2,4,8} ✉

Systemic lupus erythematosus (SLE) is a life-threatening autoimmune disease characterized by adaptive immune system activation, formation of double-stranded DNA autoantibodies and organ inflammation. Five patients with SLE (four women and one man) with a median (range) age of 22 (6) years, median (range) disease duration of 4 (8) years and active disease (median (range) SLE disease activity index Systemic Lupus Erythematosus Disease Activity Index: 16 (8)) refractory to several immunosuppressive drug treatments were enrolled in a compassionate-use chimeric antigen receptor (CAR) T cell program. Autologous T cells from patients with SLE were transduced with a lentiviral anti-CD19 CAR vector, expanded and reinfused at a dose of 1×10^6 CAR T cells per kg body weight into the patients after lymphodepletion with fludarabine and cyclophosphamide. CAR T cells expanded in vivo, led to deep depletion of B cells, improvement of clinical symptoms and normalization of laboratory parameters including seroconversion of anti-double-stranded DNA antibodies. Remission of SLE according to DORIS cri-

► CAR-T CELL THERAPY

- In 2022, CAR T cell trial in severe, treatment refractory lupus. **ALL treated patients went into remission**
- Multiple efforts ongoing to develop anti-CD19 CAR-T cell therapy in MS
- Last week, Kyverna granted fast track status by FDA to pursue CAR T in MS (KYV-101).

Kyverna's CAR T-Cell Therapy Candidate Cleared for Phase 2 Trial in Progressive MS

January 12, 2024

Rosanna Sutherby, Pharm.D.

News

Article



The CAR T-cell therapy targets the CD19 protein ubiquitous on the surface of B cells, which are known to mediate various types of autoimmune diseases, including MS.

California-based Kyverna Therapeutics recently [announced](#) the FDA approval for its investigational CAR T-cell therapy KYV-101 to proceed to a phase 2 study in patients with refractory progressive multiple sclerosis (MS).

Stem Cell

2023 publication looking at 231 patients with RRMS who underwent aHSCT in Sweden.

5.5 years median follow up duration

73% achieved NEDA (no evidence of disease activity)

No deaths. Grade 3 Adverse Events 1.7% of patients.

This treatment is ONLY proven in relapsing MS

BEAT-MS trial underway in US
Compares aHSCT to high efficacy therapies



► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/jnnp-2023-331864>).

For numbered affiliations see end of article.

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Original research

Haematopoietic stem cell transplantation for treatment of relapsing-remitting multiple sclerosis in Sweden: an observational cohort study

Thomas Silfverberg^{1,2}, Christina Zjukovskaja,³ Per Ljungman,^{4,5} Adjmal Nahimi,⁶ Erik Ahlstrand,⁷ Arta Dreimane,⁸ Sigrun Einarsdottir,^{9,10} Jan Fagius,³ Ellen Iacobaeus,^{11,12} Hans Hägglund,^{3,5} Niclas Lange,⁷ Stig Lenhoff,¹³ Jan Lycke¹⁴, Johan Møllergård,^{15,16} Fredrik Piehl,^{11,12} Anders Svenningsson,^{17,18} Andreas Tolf³, Honar Cherif,³ Kristina Carlson,³ Joachim Burman³

ABSTRACT

Background A growing evidence base supports the use of autologous haematopoietic stem cell transplantation (aHSCT) for treatment of relapsing-remitting multiple sclerosis (RRMS), but it has not yet been integrated into most national clinical guidelines. The objective of this study was to assess efficacy and safety when aHSCT is implemented in routine healthcare.

Methods We assessed 231 patients and the final analysis included 174 RRMS patients who were treated with aHSCT in Sweden before 1 January 2020. Efficacy was evaluated by performing a retrospective analysis of prospectively collected data from the Swedish MS registry. Procedure-related safety was assessed by analysing data from electronic patient records covering a period of 100 days following aHSCT.

Results With a median follow-up time of 5.5 (IQR: 3.4–7.5) years, the Kaplan-Meier estimate for no evidence of disease activity was 73% (95% CI 66% to 81%) at 5 years and 65% (95% CI 57% to 75%) at 10 years. Out of the 149 patients with baseline disability, 80 (54%) improved, 55 (37%) were stable and 14 (9%) deteriorated. The mean number of adverse events per patient was 1.7 (±SD: 1.5) for grade 3 events and 0.06 (±SD: 0.3) for grade 4 events. Febrile neutropenia was the most common adverse event, affecting 68% of patients. There was no treatment-related mortality.

Conclusions Treatment with aHSCT for RRMS is associated with freedom from disease activity in a majority of patients, with acceptable adverse events. This procedure should be considered a standard of care for patients with highly active RRMS.

INTRODUCTION

Multiple sclerosis (MS) is a leading cause of permanent neurological disability in young adults.¹ The prevailing theory posits that MS is an autoimmune

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Autologous haematopoietic stem cell transplantation (aHSCT) is an emerging treatment option for relapsing-remitting multiple sclerosis (RRMS) patients. To date, only one randomised clinical trial has compared aHSCT with standard disease-modifying treatment (DMT) for RRMS. This trial demonstrated a significant advantage of aHSCT over standard DMT in terms of time to progression and neurological disability after 2 years. Moreover, there were no recorded Common Terminology Criteria for Adverse Events grade 4 adverse events or instances of treatment-related mortality. However, it remains uncertain whether these results can be translated into routine healthcare.

WHAT THIS STUDY ADDS

⇒ This study supports and strengthens the evidence from the sole randomised controlled trial on aHSCT for RRMS conducted thus far. More than half of the participants experienced improved disability, and approximately two-thirds displayed no evidence of disease activity over a 10-year period. The incidence of severe adverse events was low, and there was no record of treatment-related mortality, suggesting that aHSCT can be safely implemented within routine healthcare.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ aHSCT has the potential to benefit a larger number of MS patients and should be considered a standard of care for highly active MS. Further research is needed to identify the specific patient populations that would derive the most benefit from aHSCT.

- ▶ We MUST find more effective treatments for progressive MS
- ▶ MS cure also means to restore function that has been lost
- ▶ Future therapies must:
 - Penetrate the brain
 - Target smoldering inflammation
 - Address EBV infection
 - Address remyelination and repair

Final Thoughts