MULTIPLE SCLEROSIS JOURNAL | MSJ

Review

Aggressive MS and Autologous HSCT: A review on behalf of the Autoimmune Diseases Working Party of the European Society for Blood and Marrow Transplantation

Multiple Sclerosis Journal

1–16

DOI: 10.1177/13524585251349129

Giacomo Boffa*, Angela Genchi*, Alice Mariottini, Gavin Brittain, John Snowden, Tobias Alexander, Manuela Badoglio, Elisa Roldan Galvan, Paolo A Muraro, Basil Sharrack, Riccardo Saccardi, Matilde Inglese, Lucia Moiola and Raffaella Greco

Abstract: Multiple sclerosis (MS) presents a spectrum of disease activities, making prognostication and treatment challenging. Our focus on aggressive MS (AMS), a subset lacking a universally accepted definition, aims to clarify its identification and management. Here we critically dissect the different criteria for defining AMS based on the latest research and consensus, the early prognostic factors which can unambiguously identify aggressive variants early in the disease course and the available high-efficacy therapies, with a special focus on autologous haematopoietic stem cell transplantation (AHSCT), which is considered a standard of care for relapsing-remitting MS refractory to disease-modifying treatments. The review explores the potential of tailoring AHSCT protocols to individual risk and disease activity profiles, suggesting a personalized approach that could optimize treatment efficacy and safety. While awaiting the results of ongoing randomized clinical trials, AHSCT should be considered for patients with poor prognostic factors early in the disease course, in case of suboptimal response to disease-modifying therapies, but also in naïve patients with AMS experiencing rapid disability accrual.

Keywords: Aggressive multiple sclerosis, highly active multiple sclerosis, high-efficacy therapies, autologous haematopoietic stem cell transplantation

Date received: 31 January 2025; revised: 14 May 2025; accepted: 23 May 2025

Correspondence to:
G Boffa
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Largo Paolo Daneo 3, Genoa 16132, Italy.
giacomo.boffa@unige.it

A Genchi
Department of Neurology, IRCCS San Raffaele Hospital, Via Olgettina, 60, 20132 Milan, Lombardia, Italy.
genchi.angela@hsr.it

Giacomo Boffa
Matilde Inglese
Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy; IRCCS Ospedale Policlinico San Martino, Genoa, Italy

Angela Genchi
Department of Neurology, IRCCS San Raffaele Hospital, Milan, Italy; Vita-Salute San Raffaele University, Milan, Italy

Alice Mariottini
Department of Neurosciences, Drug and Child Health, University of Florence, Florence, Italy; Tuscan Region Multiple Sclerosis Referral Centre, Careggi University Hospital, Florence, Italy

Gavin Brittain
Basil Sharrack
Department of Neurology, Sheffield Teaching Hospitals NHS Foundation Trust & Division of Neurosciences, University of Sheffield, Sheffield, UK

John Snowden
Elisa Roldan Galvan
Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust,

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune-driven, inflammatory and degenerative disorder of the central nervous system. MS is very challenging to prognosticate since it is characterized by heterogeneous symptoms, disease course and outcomes. Traditionally, relapsing-remitting MS (RRMS) has been classified according to disease severity into mild, moderate and aggressive (referred to as malignant, highly active or rapidly evolving severe) MS, although the spectrum of MS disease activity is variable among patients and within the same patient over time. To date, no accepted definitions for aggressive MS (AMS) exist and its prevalence differs significantly according to the criteria applied and the timing of the measurement. Predicting a person's long-term disease outcome at the onset of MS is highly desirable but is not yet possible. Precise stratification of patients based on disease severity would aid in initiating the most appropriate disease-modifying therapy (DMT) preventing disability accrual. Among high-efficacy therapies (HETs), autologous hematopoietic stem cell transplantation (AHSCT) has been extensively explored as a treatment option for patients with treatment-resistant MS. Current data strongly support the notion that early administration of AHSCT yields the most favourable outcomes, especially in younger patients with short illness duration and lower levels of disability. Given that AHSCT has the potential for severe adverse events, identifying patients at high risk of AMS early in their disease trajectory is paramount. In this review, we aim to summarize the available evidence on definitions of AMS and prognostic markers that could aid in identifying the best candidates for early HETs, including AHSCT. We will also discuss the position of HETs, including AHSCT, within the

University of Sheffield, Sheffield, UK; Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, UK

Tobias Alexander
Department of Rheumatology and Clinical Immunology, Charité University Hospital Berlin, Berlin, Germany

Manuela Badoglio
EBMT Paris Study Office, Department of Haematology, Hôpital Saint-Antoine, Paris, France

Paolo A Muraro
Department of Brain Sciences, Imperial College London, London, UK

Riccardo Saccardi
Cell Therapy and Transfusion Medicine Unit, Careggi University Hospital, Florence, Italy

Lucia Moiola
Department of Neurology, IRCCS San Raffaele Hospital, Milan, Italy

Raffaella Greco
Vita-Salute San Raffaele University, Milan, Italy; Unit of Haematology and Bone Marrow Transplantation, IRCCS San Raffaele Hospital, Milan, Italy

*Co-first authors

current MS treatment algorithm, focusing on patient selection and predictors of better response to AHSCT. Moreover, we will explore the potential for personalizing AHSCT based on the patient's disease activity and risk profile.

AMS: Challenges in definition and prognostication

AMS is characterized by severe relapses, rapid disability progression and poor response to standard treatments. Several criteria have been employed in research and clinical practice to prospectively identify such patients. The proportion of patients affected by AMS varies significantly depending on the definition used, ranging from 4% to 23%, with little overlap between these definitions.[1,2] There are several challenges when categorizing disease severity in MS. First, the severity of the disease is likely influenced by various pathophysiological processes, including not only inflammatory mechanisms,[3] but also central nervous system (CNS)-intrinsic biological processes[4] such as mitochondrial function, synaptic plasticity, oligodendroglial biology[5,6] which profoundly influence the extent and rate of neurodegeneration and the CNS compensatory capability (for both repair and neuroplasticity). These processes vary significantly among individuals, evolve over time and are at least partly independent of one another.[7,8] In a similar way, overall disability progression in MS can be driven by the residual disability accumulated after relapses (relapse-associated worsening (RAW))[9] and/or by a subtle progression occurring independently of relapses (progression independent of relapse activity (PIRA)[10] or smouldering associated worsening)[11]. To address this complexity, it has been proposed to distinguish between highly active MS (HAMS) and AMS.[12] The former term refers to acute, severe CNS inflammation (causing high relapse frequency and high radiological burden of new/gadolinium enhancing lesions) responsible for heightened disease severity (mainly RAW) in the short term, while the latter encompasses both inflammatory (RAW) and neurodegenerative (PIRA) components, leading to accelerated accrual of disability if not promptly treated (mainly PIRA) (Figure 1). Second, while identifying early predictive markers of risk at disease onset is crucial, continuously assessing disease severity over time is essential. An aggressive/highly active disease course may suddenly emerge after years of disease stability, such as following changes in treatment or during pregnancy or due to an, yet, unexplained change in the underlying pathophysiology of the disease. Identifying such changes promptly allows for rapid adjustment of therapeutic approaches to better manage the evolving disease course. Third, atypical demyelinating syndromes, such as tumefactive demyelination, Baló's concentric sclerosis and Marburg's disease, have been historically considered part of the spectrum of AMS. Whether the clinical, radiological and pathological differences between these entities are significant enough to classify them as separate diseases remains uncertain,[13] it is possible that tumefactive demyelination and Baló's concentric sclerosis could instead represent various lesion types encountered in the context of both MS and other demyelinating diseases. A wide spectrum of possible long-term outcomes can occur after an aggressive disease onset, ranging from relatively mild-moderate to fulminant diseases. Therefore, the terms 'tumefactive MS', 'Baló's concentric sclerosis' and 'Marburg's disease' should be used with caution when discussing AMS and making prognostications about disease course.

An early attempt to establish a definition for AMS revolved around the rate of disability accrual measured by the Expanded Disability Status Scale (EDSS). Some researchers defined AMS as reaching an EDSS score of 6 within 5 years[14,15] or 10 years[16] from the onset of disease. Others proposed less stringent criteria, requiring an EDSS score of 4 within 5 years of symptom onset.[17] In addition to disability progression, some authors suggested that a core feature of AMS was a gain of two or more EDSS points over a 2-year period.[18,19] As the expansion of DMTs changed the landscape of MS management, definitions of AMS attempted to incorporate the response to treatment as a marker of disease severity. For example, Edan et al., conducted a clinical trial on the induction effect of mitoxantrone and defined AMS as the presence of 2 or more relapses and at least one gadolinium-enhancing (Gd+) lesion despite active treatment.[19] Similarly, Saccardi et al., aimed to identify patients eligible for AHSCT, referred to HAMS as failure of at least one and up to three DMTs evidenced by ongoing or increased clinical and magnetic resonance imaging (MRI) activity.[20]

As patients with AMS rapidly accrue disability, they have a narrow therapeutic window necessitating prompt and early identification and should be quickly considered for HETs. A recent registry-based study[1] identified indicators that, if observed in the first year since symptom onset, convey increased risk of the patient meeting criteria for AMS (EDSS of 6 within 10 years from disease onset). Specifically, (1) age $>$ 35 years at symptom onset, (2) EDSS $\geq$ 3, and (3) pyramidal symptoms within the first year were associated with AMS. Age of onset and disability in the first year were confirmed to be associated with

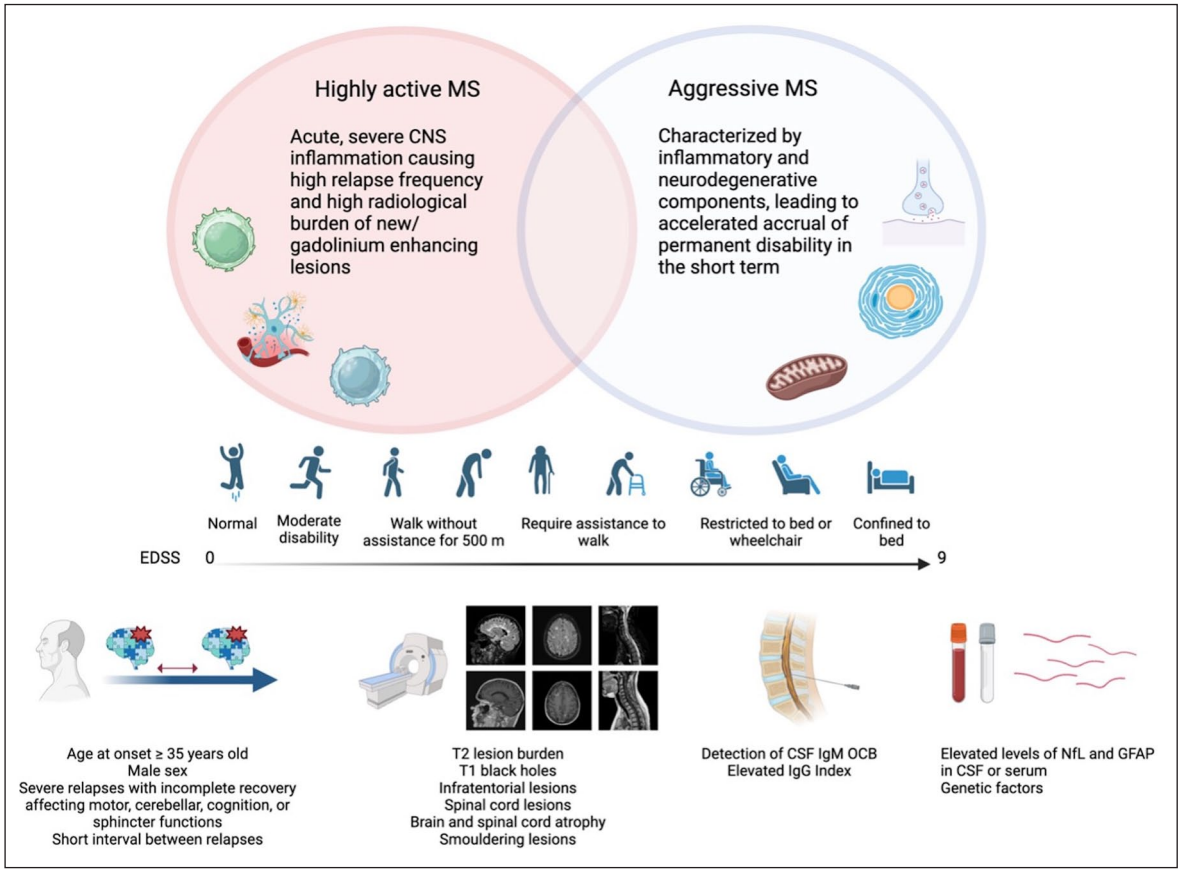

Figure 1. Differences between 'highly active MS', characterized by severe CNS inflammation responsible for heightened disease severity in the short term, and 'aggressive MS', encompasses both inflammatory and neurodegenerative components. Clinical, radiological and biological markers predicting the risk of highly active and aggressive MS. *Created with BioRender.com*

AMS in an independent cohort of patients.[2] Interestingly, these variables were predictive of AMS in both relapsing-remitting patients and people with progressive MS.[2] Another study by Bose et al. explored various clinical and radiological variables assessed within 3 years from disease onset.[21] They developed a 10-item model of clinically accessible markers, including age of onset, EDSS score, pyramidal, cerebellar and bowel/bladder symptoms, walking speed, attack recovery and time to DMT initiation, that accurately predicted AMS at 10 years. In addition, Gasperini et al. investigated predictive factors of AMS in patients treated with interferons and glatiramer acetate and found that a score composed of age at onset, disease duration, EDSS score and response to DMT could detect AMS patients at 10 years.[22] Besides clinical data, some studies aimed to identify baseline MRI characteristics that could predict a later AMS course.[16] Tintoré and colleagues showed that early radiological biomarkers associated with AMS were the presence of ⩾20 lesions on T2-weighted images or ⩾2 Gd+ lesions at baseline MRI. Moreover, other easily accessible MRI parameters, such as the presence of spinal lesions (symptomatic or asymptomatic), have been reported as markers of early and long-term disability accrual.[23] Other biomarkers include, but are not limited to, chronic active lesions, IgM oligoclonal bands in the cerebrospinal fluid, serum neurofilament light chain and glial fibrillary acidic protein (GFAP) levels.[24–26] A 2018 focused workshop of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) on AMS reported that no consensus could be achieved on a definition of AMS, also because of unavailable data correlating aggressive disease with imaging and molecular biomarkers.[27] It is likely that in the near future, the combined use of these biomarkers and clinical endpoints, as a composite measure, will help identify and discriminate between patients with HAMS and AMS (Figure 1). However, to date, their clinical implementation is limited and requires further investigation.

Long-term outcomes of available induction strategies in AMS

There are currently no evidence-based criteria to guide the selection of the best treatment approach for patients with AMS.[28] Notably, the recently updated guidelines from the American Academy of Neurology[29] and the European Academy of Neurology/ECTRIMS[30] do not provide specific recommendations for managing patients with AMS. One significant challenge of obtaining high-quality evidence on the best treatment strategy in AMS is the underrepresentation of these patients in typical randomized clinical trials (RCTs). This issue arises due to the reduced incidence of AMS patients within the MS population, the specific inclusion and exclusion criteria of clinical trials and the ethical dilemma of treatment randomization in cases of aggressive and fast-progressing disease. Thus, the correct therapeutic approach to patients with RRMS still represents a challenge, given the broad spectrum of therapies and the evaluation of risk/benefit balance. The treatment algorithm in MS has evolved in the last few years. Two ongoing RCTs (TREAT-MS, NCT03500328 and DELIVER-MS, NCT03535298) are comparing early HETs versus the traditional escalation approach (starting with safer but lower-efficacy therapies before escalating to HETs only in cases of suboptimal response) for preventing long-term disability in RRMS. While awaiting the results of these RCTs, data regarding the long-term outcomes following early HETs has been acquired from subgroup analyses of pivotal trials and retrospective studies, showing that this treatment strategy could limit disease progression from the earliest phases of the disease, reducing the accumulation of irreversible clinical disability,[31–35] the evolution to secondary progressive MS (SPMS),[36] and the progression of brain atrophy.[37] These observations challenged the traditional escalation strategy, suggesting early use of HET which aims to rapidly obtain a control of inflammatory activity is likely to provide more robust radiological and clinical efficacy. Choosing the appropriate treatment strategy is even more relevant in patients with AMS, where the primary therapeutic aim is moving towards preventing CNS degeneration and irreversible disability, conditions for which the window of therapeutic opportunity is narrow.

The classification of DMTs as moderate-efficacy therapies (METs) and HETs is not universally agreed[30,38–40] due to the presence of different definitions of 'highly effective' and to the marketing of new DMTs, the effectiveness of which is defined by phase III trials with differences in study design (comparator arm treatments, outcome measures, inclusion criteria and baseline patient characteristics). Based on the average relapse reduction, the 2015 Association of British Neurologists (ABN) guidelines[41] divided DMTs into two broad classes: high efficacy, with an annualized relapse rate (ARR) reduction more than 50% (alemtuzumab (LEM) and natalizumab (NAT)) and moderate efficacy, defined as ARR reduction between 30% and 50% (dimethyl fumarate, fingolimod, glatiramer acetate, IFN-β preparations and teriflunomide). In the ABN guidelines, several newer DMTs (ocrelizumab (OCR), ofatumumab (OFA), cladribine, ozanimod, siponimod) have not been included. A recent Expert Opinion paper[42] agreed that the definition of HET should take into account not only the therapeutic effect on the average of relapse reduction, but also the effect on MRI inflammatory activity (new/enlarging T2-hyperintense lesions and/or Gd+ lesions) and outcome measures of disease progression (decrease of clinical disability progression, of MRI measures of neurodegeneration and of serological biomarkers). A suggestion was made to consider treatments as HETs that result in an average reduction of ARR higher than 50%, of MRI activity ⩾70%, and of disability progression more than 30%. This definition allows a more comprehensive evaluation of the DMT therapeutic effect given the higher sensitivity of MRI measures than clinical evaluation of disease activity and the importance of preventing disease progression.

NAT is a humanized monoclonal antibody that binds to the alpha 4 chain of the VLA-4 integrin (CD49d), preventing leukocyte trafficking through the brain–blood barrier into the CNS parenchyma. The NAT efficacy and safety have been demonstrated in a placebo-controlled phase 3 study (AFFIRM)[43] and in a second phase 3 clinical study (SENTINEL) in combination with interferon beta-1a (IFNβ-1a).[44] A post hoc analysis of data from the AFFIRM and SENTINEL data trials[45] was performed to assess the efficacy of NAT in a subgroup of patients with HAMS, defined as having ⩾2 relapses in the year prior to study entry and ⩾1 Gd+ lesion on T1-weighted MRI at baseline). In the AFFIRM study, 148 patients receiving NAT and 61 receiving placebo met the criteria for treatment-naïve relapsing HAMS, demonstrating reductions of 81% in ARR, 53%–64% in sustained disability progression and 84% in the mean number of gadolinium-enhancing lesions. In the SENTINEL study, 74 patients receiving combination therapy and 95 receiving IFNβ-1a monotherapy met the criteria for HAMS despite prior IFNβ treatment, displaying reductions of 76% in ARR, 58%–61% in sustained disability progression and 96% in the mean number of gadolinium-enhancing lesions. Notably, NAT's effect in slowing disability progression is more evident in patients with

highly active disease, probably due to the higher risk of these patients to rapidly accumulate disability. Therefore, NAT is used in the treatment of patients with rapidly evolving, highly active forms of relapsing MS, regardless of prior treatment.

LEM is a humanized monoclonal antibody targeting CD52, inducing a rapid lymphocyte depletion, followed by slow repopulation from unaffected precursor cells with quantitative and qualitative immune changes, enabling a rebalancing of immune-tolerance networks. LEM's efficacy has been tested in two phase III studies, the CARE-MS I (naïve patients) and II (patients with breakthrough disease despite previous DMTs), with IFNβ-1a as an active comparator[46,47] with extension studies demonstrating a durable effect on relapse rate, disability and MRI activity.[48] A post hoc analysis[49] evaluated the efficacy of LEM at 9 years in CARE-MS patients who met criteria for HAMS. Given the absence of a consensus definition for HAMS, a primary definition (⩾2 relapses in the year prior to baseline and ⩾1 Gd+ lesion at baseline) and three alternative definitions (1]⩾2 relapses in the year prior to baseline; 2] ⩾1 relapse in the year prior to baseline and ⩾3 Gd+ lesions at baseline; 3] ⩾1 relapse in the year prior to baseline and ⩾1 Gd+ lesion at baseline while on therapy with another DMT) were applied, demonstrating higher efficacy of LEM than IFNβ-1a in clinical and radiological measures of disease activity over 2 years in patients with highly active RRMS. Moreover, LEM may help to control HAMS patients for at least 7 additional years. Notably, the sensitivity analyses on patients meeting some alternative definitions focused on either higher MRI lesion counts (2) or disease activity while on prior therapy (3), compared to patients meeting the primary definition, and showed a reduced efficacy for some endpoints (a greater EDSS score increase through year 9, lower relapse-free or sustained NEDA (No Evidence of Disease Activity) over years 3–9, lower MRI disease activity-free), with more patients requiring additional LEM compared with the overall CARE-MS population.

Anti-CD20 monoclonal antibodies, rituximab (RTX, chimeric), OCR (humanized), OFA (fully human) and ublituximab (UBL, glycoengineered, chimeric) selectively deplete CD20 B cells. Despite the absence of phase 3 trial, RTX has been widely used based on favourable efficacy data observed in the HERMES phase 2 study.[50] In addition, a retrospective multicentre study[51] demonstrated the RTX efficacy in patients with refractory highly active RRMS (⩾new T2 lesion and/or Gd+ lesion despite immunosuppressive DMT, fingolimod, NAT or mitoxantrone). OCR was studied in two identical randomized controlled trials (OPERA-I and OPERA-II), compared to IFNβ-1a.[52] A subgroup analysis from the pooled OPERA-I and OPERA-II populations[53] demonstrated the OCR efficacy in pre-treated patients with active MS (either ⩾1 relapse in the year prior to randomization or ⩾1 baseline Gd+ lesion) and HAMS (defined as ⩾1 relapse in the year prior to randomization and ⩾9 T2 lesions or ⩾1 T1 Gd+ lesion at baseline). In these populations of patients, OCR significantly reduced the ARR by 65% and 68%, the disability progression by 54% and 53%, the T1 Gd+ lesions by 98%, and new or enlarging T2 lesions by 80%. OFA and UBL have been tested, in comparison to teriflunomide, in ASCLEPIOS-I and ASCLEPIOS-II,[54] and ULTIMATE-I and ULTIMATE-II,[55] respectively, demonstrating efficacy outcomes similar to OCR. To our knowledge, data about the OFA and UBL in patients with HAMS are not already available. Although these studies provide valuable insights into the efficacy of HETs in patients with HAMS, they do not yield evidence regarding the effectiveness of these treatments in individuals with AMS or in patients who have already failed a prior course of HET. As these populations are typically excluded from RCTs, there is an urgent need to establish a consensus on the definition and therapeutic management of AMS. Such efforts are essential to guide clinical decision-making and to ensure the optimal care of patients at high risk of rapid disease progression and irreversible disability accumulation.

Efficacy and safety outcomes of AHSCT in AMS

Intense immunosuppression followed by hematopoietic stem cell transplantation has gained increasing attention as a standard of care for patients with highly active RRMS failing DMTs and is a recommended clinical option for AMS not previously treated with a full course of DMT.[56,57] Recently, a joint ECTRIMS/European Group for Blood and Marrow Transplantation (EBMT) consensus statement, providing practical guidance and recommendations on the use of AHSCT in MS, has been published.[57] Comprehensive reviews on the efficacy of AHSCT in MS patients have been published elsewhere.[58–60] Here we aimed to focus on the main studies focusing on the use of AHSCT versus HETs in patients with HAMS and/or AMS. Das et al. reported the only case series of patients (n = 20) with treatment-naïve AMS (defined as ⩾2 relapses in the previous 12 months with incomplete recovery and ⩾1 new or enlarging T2 or Gd+ MRI lesion) treated with AHSCT as a first-line treatment. Once a re-baseline MRI had been

undertaken at 6 months post AHSCT, NEDA was achieved in 100% of patients, with an improvement of the median EDSS from 5.0 to 2.0 after a median of 30 months follow-up.[61] The 2019 phase III MIST study[62] included 110 RRMS patients with ⩾2 relapses or 1 relapse and Gd+ lesion(s) within the previous year despite receiving DMT, and an EDSS score between 2.0 and 6.0, and randomized them 1:1 to AHSCT with an intermediate intensity lymphoablative regimen (cyclophosphamide + ATG) or to the best available platform DMT. Progression occurred in 3 of the AHSCT patients and 34 of the DMT control group, with the EDSS in the AHSCT group at 2 years stable or improved in 94.5%. NEDA at 5 years was 78.5% in the AHSCT group compared to 2.97% in the DMT group. The control DMT group included a high proportion of patients treated with glatiramer acetate, IFN-β drugs and fingolimod and few with NAT. No patients in the control group were treated with OCR, OFA or LEM due to the historical nature of the trial. In a retrospective Italian study, Boffa et al. compared the efficacy of AHSCT with BEAM + ATG protocol and LEM in a population of patients with AMS (defined as ⩾2 relapses with incomplete resolution in the past year, or > 2 MRI scans showing new or enlarging T2 lesions or Gd+ lesions despite DMTs, or an EDSS score ⩾4 within 5 years of symptom onset despite DMTs for at least 1 year). Despite worse baseline characteristics in the transplanted patient group (higher EDSS [6.0 vs. 3.0], ARR [3.2 vs. 1.7] and baseline MRI activity [88% vs. 43.8%]), NEDA was achieved more often in AHSCT patients (75% vs. 56%) with a significantly lower ARR (0.05 vs. 0.35) compared to the LEM population.[63] These results were confirmed by two independent real-world studies (using CY + ATG and BEAM + ATG conditioning regimens),[64,65] confirming that AHSCT significantly reduced the risk of relapses and MRI activity, allowing NEDA status in a higher proportion of AMS patients compared with LEM. Recently, two large retrospective studies[66,67] comparing AHSCT versus HETs (NAT and OCR) and HETs (LEM and OCR), respectively, have been published. Using data from an international registry and from 6 centres experienced in the use of AHSCT in MS, Kalincik and colleagues[66] compared 146 patients treated with AHSCT (mean EDSS = 3.86; pre-treatment ARR = 0.82) versus 730 matched patients treated with NAT (mean EDSS = 3.88; pre-treatment ARR = 0.86), through propensity score matching, and found that AHSCT was more effective in reducing relapse rate than NAT and was associated with a higher rate of recovery from disability over 5 years. In a similar way the authors compared 110 patients treated with AHSCT versus 343 matched patients treated with OCR and did not find evidence for difference in the effectiveness of AHSCT and OCR, although over a shorter available follow-up (3 years). Muraro et al.[67] retrospectively analyzed clinical outcomes of propensity score matched patients with HAMS [defined as RRMS patients experiencing treatment failure with at least one licenced DMT of high efficacy, defined as evidence of relapse or EDSS score increase and MRI activity (⩾1 Gd+ lesion or ⩾2 new T2 lesions on MRI within the previous 12 months), after being on treatment for at least 6 month] treated with AHSCT, LEM or OCR. AHSCT was found to induce a lower relapse rate compared to LEM and OCR, with lower MRI activity compared to LEM. No difference was observed in the risk of EDSS progression compared to LEM and OCR. It is worth noting that, in the OCR group, the proportion of patients lost to follow-up at 3 years is significantly higher than that observed in patients treated with AHSCT, with a reduction of approximately 67% in the OCR group and around 44% in those undergoing AHSCT.

Although the considerable heterogeneity of AHSCT protocols analyzed in these retrospective studies, along with their limited sample sizes, makes it difficult to draw definitive conclusions regarding the efficacy of AHSCT compared to HETs, these studies collectively support the reasonable, fair and ethical implementation of ongoing RCTs comparing AHSCT with OCR and modern HETs[68] (Table 1). However, it is important to note that, since these trials also include patients with HAMS rather than strictly AMS, harmonizing results across studies is essential to clearly define the role of AHSCT in the treatment of AMS patients.

Efficacy and safety of the different AHSCT conditioning: personalizing AHSCT to the patient's disease activity?

The classification of disease severity in MS is a major challenge due to its continuum spanning from stable to aggressive disease forms. An effective therapeutic strategy which is customizable according to individual patient characteristics to maximize benefits and minimize risks, would be a considerable advantage. Despite the relative differences in immunosuppression intensity of different AHSCT conditioning regimens represent a continuum,[69] historically they have been classified into three grades of intensity according to the extent of immunoablation induced.[56,70] Indirect comparisons suggest a trend for superior effectiveness of higher over lower intensity regimens, but these are hampered by differences in patient population and epoch of the treatments across studies, and no head-to-head comparisons are available yet.[71–73]

Table 1. Inclusion and exclusion of current phase III randomized controlled trials of aHSCT in MS.

Trial name	Registry identifier	Select inclusion criteria	Location	Conditioning regimen	Active comparators
BEAT-MS	NCT04047628	1. Age ⩾16 to ⩽55 2. RRMS or SPMS 3. EDSS 0 to ⩽ 6.0 4. ⩾2 relapses OR 1 relapse and ⩾2 active MRI lesions[a], in the last 24 months with 1 episode occurring in the last 12 months, despite DMT use, excluding interferons and glatiramer acetate	United states and United Kingdom	BEAM and rabbit ATG	Alemtuzumab, cladribine natalizumab ocrelizumab, ofatumumab or rituximab.
NET-MS	EudraCT Number: 2022-002654-95	1. RR-MS 2. Treatment-resistant MS, defined as the occurrence of disease activity following ⩾6 months of treatment with an oral agent or a monoclonal antibody in the 12 months prior to the screening visit. Disease activity is defined as: (1) the occurrence of ⩾1 relapse AND (2) the occurrence of MRI evidence of disease activity, defined as one or more gadolinium-enhancing lesion(s) or one or more new non-enhancing T2 lesion(s) compared to a reference scan obtained not more than 18 months prior to the screening visit. 3. Age ⩾18 and ⩽55. 4. Expanded Disability Status Scale (EDSS) ⩾2.0 and ⩽6.0. 5. Candidacy for treatment with at least one of the following DMT: natalizumab, alemtuzumab ocrelizumab and/or ofatumumab. Candidacy must include no prior treatment failure with the candidate DMT and no contraindication to the candidate DMT.	Italy	BEAM and rabbit ATG	natalizumab (Tysabri®), alemtuzumab (Lemtrada®) ocrelizumab (Ocrevus®) and ofatumumab (Kesimpta®).
RAM-MS	NCT03477500	1. Age ⩾18 to ⩽50 2. RRMS 3. EDSS 0 to ⩽5.5 4. ⩾1 relapse treated with steroids AND ⩾1 Gd enhancing MRI lesion, OR ⩾3 new or enlarging T2 lesions, despite ⩾3 months of DMT[b], in the last 12 months	Scandinavia	Cy (2.0 g/m^2) and rabbit ATG	Alemtuzumab, cladribine or ocrelizumab
StarMS	ISRCTN88667898	1. Age ⩾16 to ⩽55 2. RRMS 3. EDSS 0 to ⩽6.0 (⩽1.5 must fulfill additional criteria)[c] 4. ⩾1 relapses or ⩾2 new or enlarging T2 lesions despite any non-comparator DMT use, or RES MS[d] in treatment-naïve patients, in the last 12 months 5. <10 years symptom duration	United Kingdom	Cy (2.0 g/m^2) and rabbit ATG	Alemtuzumab, cladribine, ocrelizumab or ofatumumab

ATG = anti-thymocyte globulin, BEAM = carmustine (BCNU), etoposide (VP-16), cytarbine (Ara-C) and melphalan, Cy = cyclophosphamide, DMT = disease-modifying treatment, EDSS = Expanded Disability Status Score, Gd = gadolinium, MRI = magnetic resonance imaging, RRMS = relapsing-remitting multiple sclerosis, SPMS = secondary progressive multiple sclerosis.
[a]Gd enhancing lesion or new T2 lesion in the last 24 months.
[b]Excluding alemtuzumab, cladribine, mitoxantrone, ocrelizumab and rituximab.
[c]Less than 5 years illness duration, ⩾2 relapses in previous 12 months, ⩾2 Gd enhancing MR lesion, high brain lesion load and brain or spinal cord atrophy.
[d]Two or more disabling relapses in 1 year, and ⩾1 Gd enhancing lesions or a significant increase in T2 lesion load on brain MRI.

High-intensity regimens encompass the use of total body irradiation (TBI) or busulfan, typically associated with Cy and ATG. TBI-based regimens were used in early AHSCT studies including patients with progressive and advanced disease, showing overall poor neurological outcomes.[74–76] Despite busulfan-based regimens inducing a long-lasting and radical suppression of clinical and MRI inflammatory activity, higher toxicity, with severe adverse events in 8% of the cases and a 4% risk of treatment-related mortality (TRM), were reported in the same study.[77] In EBMT guidelines, high-intensity protocols are no longer recommended in MS patients (except in a clinical trial setting) due to concerns for short- and long-term toxicity,[78] including possible radiation-related neurotoxicity.[74,79]

Intermediate-intensity regimens include myeloablative protocols (inducing ablation of bone marrow haematopoiesis and requiring stem cell support), such as BEAM-ATG, and non-myeloablative (or lymphoablative) regimens, such as Cy (200 mg/Kg)-ATG. The use of either BEAM-ATG or Cy-ATG is currently recommended for the treatment of MS, with the latter increasingly used over the last decade.[56] In studies adopting BEAM-ATG as a unique or predominant regimen, and including different proportions of RR- and SP-MS, rates of relapse-free survival were on average higher than 80% over a mid-long-term follow-up,[71,80–84] and disability progression-free survival ranged from 70% to 90% at 3–5 years, up to 100% at year 10 in one study.[81] In a cohort of 507 RRMS patients treated with the Cy-ATG protocol, relapse-free survival was 89% at year 5, and progression-free survival was 90% at year 4.[85] In RRMS, AHSCT with Cy-ATG conditioning regimen was demonstrated to be superior to DMTs (LEM, OCR, OFA, UBL and cladribine excluded) by an RCT.[62] Importantly, the TRM of AHSCT in MS patients has reduced over time, from 7.3% during the earliest use of AHSCT (1995–2000) to 0.2% in patients treated after 2016.[73,86] This considerable reduction in TRM[87] can be attributed to several factors, including a notable shift in patient-selection criteria, increased experience and advancements in transplant techniques with a reduced use of high-intensity conditioning regimens. Despite the recent COVID-19 pandemic, the non-relapse mortality (NRM, defined as death for whatever cause, without ever experiencing relapse) remains stable around 1%[88,84] from 2015 through all the 2020, according to the recent EBMT registry data.

A retrospective analysis of the EBMT and the EBMT Autoimmune Diseases Working Party (ADWP) Registries including 1114 MS patients treated over 20 years did not show any significant differences between BEAM-ATG and Cy-ATG regimens in NEDA-3 survival, nor in major toxicity indicators, that is, time to polymorphonuclear cell engraftment and TRM; the latter was slightly higher in BEAM over Cy (2% vs. 1%), although not significantly.[89] In a retrospective multicentric study, BEAM-ATG was associated with a lower risk of NEDA failure compared to lymphoablative conditioning protocols in RR-MS and was independently associated with a higher probability of suppression of relapses and new MRI activity.[71] More recently, no differences between 33 BEAM-ATG and 141 Cy-ATG treated RR-MS patients were reported in terms of TRM (0% in both groups) and efficacy (NEDA-3 as primary outcome), although BEAM-ATG was associated with a higher frequency of severe adverse events and longer hospitalization. However, as acknowledged by the authors, the two cohorts were not directly comparable due to different treatment epochs (BEAM-ATG no longer used after 2015) and significant differences in follow-up duration (mean 10 vs. 5 years, respectively), baseline disability and inflammatory disease activity (both higher in the BEAM-ATG vs. Cy-ATG cohort).[90]

Lower-intensity regimens, such as Cy 120 mg/kg + ATG, result in suboptimal control of disease activity with the reappearance of gadolinium-enhancing lesions (although using a triple-dose of gadolinium) in six of seven treated cases over 3 years of follow-up.[91] The different immunosuppressive properties of T-cell depleting serotherapies should be considered. Despite potential immunomodulatory advantages of horse-ATG (hATG),[92–96] the majority of MS patients have been treated with rabbit ATG (rATG).[56] Indeed, hATG seems to be associated with a greater level of toxicity.[97] However, in a more recent phase 2 study assessing AHSCT in refractory MS,[80] the safety of a specific type of hATG was comparable to recent data using rATG. Current evidence suggests that low-intensity regimens, based on the administration of non-myeloablative chemotherapy drugs alone (not associated with any form of serotherapy or monoclonal antibodies), may not offer long-term control of disease activity in AMS.

Besides early toxicity,[98] the incidence of long-term adverse events[70] may differ across regimens. Neurological recovery might take over some months after the procedure, and rehabilitation may impact patients' quality of life.[99] In a recent review, the risk for secondary autoimmune diseases was reported to complicate roughly 2%–14% of AHSCT performed for an autoimmune disease, being high for LEM-containing regimens, consistent with the high rates of

these events when using LEM as monotherapy due to rapid recovery of immature and naïve B cells without adequate T-cell regulation.[100] However, this figure is probably limited by under-reporting, and more recently, no differences between BEAM-ATG and Cy-ATG were observed in a retrospective study, where treatment with AHSCT with either protocol was associated with an almost six-fold increase in the incidence of autoimmune thyroiditis compared to the reference MS population.[101] The potential neurotoxic effects of AHSCT may also vary depending on the conditioning regimen. Higher cumulative doses of busulfan – a drug known for its strong neurotoxicity – have been associated with more pronounced early brain atrophy following high-intensity AHSCT.[102] In contrast, pseudoatrophy – attributed to the rapid resolution of inflammatory oedema – has been suggested as an alternative explanation for the accelerated brain atrophy observed in patients treated with BEAM-ATG.[103] Although a direct comparison between these studies is limited due to differences in patient populations and MRI protocols, it seems that patients receiving BEAM-ATG may experience relatively less volumetric brain change during early follow-up than those undergoing high-intensity regimens.

Menses recovery in females of childbearing potential was reported in 52%–70% of MS patients treated with AHSCT using BEAM-ATG[104,105] or Cy-ATG protocols,[106] respectively, but no clear effect of the conditioning regimen was observed in one study.[106] The risk for secondary infertility may be higher after TBI-based regimens, use and cumulative exposure to definite chemotherapy drugs, as observed in the haematological setting.[107,108] Overall, the impact on gonadal function and fertility represents a major issue for young patients receiving AHSCT. Fertility-preservation strategies (gamete/embryo cryopreservation) have to be considered before the treatment, and infertility should be revisited in routine follow-up of late effects.

Limited data are available on the risk for secondary neoplasms, with a possible increased risk of haematological malignancies.[109,110] Although a higher risk of neoplasm may be associated with definite regimens (i.e. TBI-based), the small number of incident cancers and potential confounders such as age, individual risk factors and the possible contribution of previous treatments confound any conclusion in this respect at present. Overall, a recent EBMT retrospective analysis[111] reported a cumulative incidence (CI) of 10.3% secondary ADs, 3.5% secondary malignancies, 20.3% endocrine/bone complications and 13.1% cardiac complications at 10 years after autologous HSCT for autoimmune diseases. In this study, secondary ADs and endocrine/bone complications were more frequently reported in MS patients.

In conclusion, different conditioning regimens are likely associated with different efficacy and safety profiles, although the identification of clear-cut differences in retrospective settings could be hampered by heterogeneity in patient populations and treatment epoch across groups. Nonetheless, current evidence suggest that high-intensity regimens should be restricted to study protocols in highly selected patients, due to higher toxicity, while de-escalated regimens may be less efficacious.[56] Intermediate-intensity regimens ('cyclophosphamide 200 mg/kg + ATG' or 'BEAM-ATG') are therefore recommended.[57] While this remains speculative, myeloablative regimens might exert a higher anti-inflammatory effect than lymphoablative regimens, in the absence of clear indication for higher risks, and could be preferred for the treatment of AMS and patients with breakthrough disease activity. Results from ongoing RCTs also including patients with relapsing-remitting AMS and using either BEAM-ATG (NCT04047628; EudraCT Number 2022-002654-95) or Cy-ATG (NCT03477500, EudraCT Number: 2019-001549-42) protocols are awaited to provide definitive evidence. Notably, other factors contribute to the final intensity of AHSCT together with conditioning regimen per se, such as previous DMT treatments, mobilization chemotherapy, use of CD34+ cells selection or monoclonal antibodies, dosage and type of ATG. Tailoring the AHSCT protocol based on individual disease activity, patient fitness and risk factors might be an approach worth exploring, as recently recommended by a joint Consensus Statement on the use of AHSCT in MS and neuromyelitis optica spectrum disorder (NMOSD) from the EBMT and ECTRIMS.[57] This personalization could involve not only the appropriate conditioning regimen selection, but also the modulation of the priming doses of cyclophosphamide (typically ranging from 2 to 4.5 g/m^2), the best timing of HSCT in relation to previous DMTs, and the appropriate interval between mobilization and conditioning. Protocol tailoring could also take into account MS phenotype, as it could be speculated that progressive forms may generally benefit from less-intense regimens due to lower inflammatory burden, higher disability and older age, these latter factors exposing to higher periprocedural risks. The potential neurotoxicity of the conditioning regimen is another point that needs to be investigated. Furthermore, as the relative contribution of pathogenetic drivers differs across MS phenotypes, it is intriguing to envision that – in the future – the treatment protocol could be customized to target the predominant pathophysiological processes involved in each phase of the disease biology. Preclinical studies have indicated a

connection between bone marrow myelopoiesis and central nervous system inflammation and demyelination in MS.[112] Considering that myeloid cells play a key role in driving chronic inflammation in MS patients, which is closely linked to disease progression, research studies focusing on the impact of myeloablative or lymphoablative regimens on these pathogenetic mechanisms are highly desirable.

European activity of AHSCT for AMS (the EBMT Registry)

The EBMT Registry is currently the largest global database for HSCT, encompassing over 3800 patients treated with AHSCT for autoimmune and inflammatory diseases. The present status of the EBMT Registry concerning MS is summarized in Table 2 and Figure 2. There has been a consistent rise in registrations, notably in the past decade, with a gradual shift from progressive MS to RRMS over time. Among the 2200 MS patients treated with HSCT, the EBMT registry reports 48 subjects affected by 'Marburg and aggressive MS'. It is likely that patients with AMS, classified according to more recent definitions discussed in this review, are significantly underestimated in the current EBMT classification. Studies examining the prevalence of HAMS and AMS in HSCT recipients and their corresponding outcomes are warranted.

Table 2. Number of adult patients that received aHSCT for autoimmune diseases (ADs) and MS.

	Number
Total AHSCT procedures for all ADs	3831
Total numbers of AHSCT for MS	2200
Number of Marburg and aggressive MS	43
Distribution in RRMS versus other MS forms	1243/800
Overall number of EBMT centres	168

AHSCT = autologous haematopoietic stem cell transplantation, ADs = autoimmune diseases, MS = multiple sclerosis, RRMS = relapsing-remitting multiple sclerosis.

Conclusions

Although our ability to precisely predict AMS at disease onset remains incomplete, there are several important prognostic markers that can be used to early identify patients at risk. These markers include accessible variables, such as age at MS onset and disability status in the first 1–3 years of the disease. Since available evidence strongly supports the initiation of early HETs in patients presenting with poor prognostic markers, all newly diagnosed patients should be evaluated for their long-term risk of AMS. In the near future, other biomarkers are likely to be implemented in clinical practice, enhancing our capacity to identify the individual degree of MS severity in terms of neuroinflammation and neurodegeneration. This progress will facilitate a more precise identification of patients with HAMS and AMS. Among HETs, AHSCT is probably the treatment strategy that would offer the greatest benefit of an earlier and more precise identification of AMS. In addition to being a standard of care treatment for treatment-resistant HAMS, if utilized early, AHSCT has the potential to prevent disability progression in patients with AMS, for many years, if not permanently. In addition, AHSCT can be customized to address the predominant pathophysiological processes involved in the disease biology, representing a valuable choice over the other HETs. While awaiting the results of ongoing RCTs that will provide insights into the positioning of AHSCT within HETs, it is crucial for MS specialists to consider AHSCT as a viable treatment option early in the disease course, as soon as poor prognostic markers are identified, in case of suboptimal response to DMTs, but also in naïve patients experiencing rapid disability accrual.[113] The neurological and haematological communities working together pro-actively, cautiously and methodically in RCTs and other prospective studies to continuously evaluate the relative efficacy and safety of AHSCT, not only over HETs but also refining the transplant techniques, can potentially alter the disease trajectory in well-selected patients with a single-stage 'one-off' treatment and fundamentally improve outcomes for people with AMS.

Acknowledgements

We are grateful for the support by EBMT and ADWP without which this work would not have been possible. The authors thank Myriam Labopin in the EBMT Paris Office, EBMT centres for their contributions to the EBMT registry and those active in the ADWP. This work is dedicated to the memory, life and work of Riccardo Saccardi MD.

Data Availability Statement

No original data were used in the present work.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

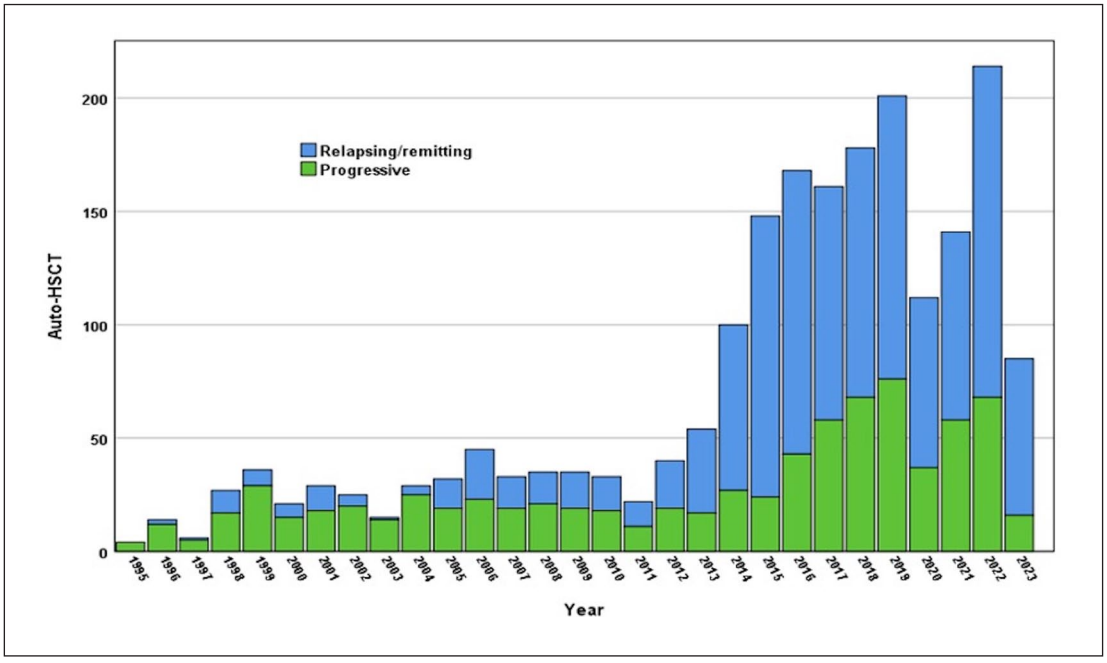

Figure 2. Autologous HSCT distribution in MS (RRMS versus other MS forms), per year (1995–2023): EBMT-ADWP registry data.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Giacomo Boffa https://orcid.org/0000-0003-2220-9422
Angela Genchi https://orcid.org/0000-0002-8573-6468
Alice Mariottini https://orcid.org/0000-0002-1869-7067
Elisa Roldan Galvan https://orcid.org/0000-0001-7242-170X
Lucia Moiola https://orcid.org/0000-0001-6313-4952

References

1. Malpas CB, Manouchehrinia A, Sharminand S, et al. Early clinical markers of aggressive multiple sclerosis. *Brain* 2020; 143(5): 1400–1413.
2. Ellenberger D, Flachenecker P, Fneishand F, et al. Aggressive multiple sclerosis: A matter of measurement and timing. *Brain* 2020; 143(5): e97.
3. Rodriguez S, Couloume L, Ferrant J, et al. Blood immunophenotyping of multiple sclerosis patients at diagnosis identifies a classical monocyte subset associated to disease evolution. *Front Immunol* 2025; 15: 1494842.
4. Tolentino M, Pace F, Perantie DC, et al. Cerebrospinal fluid biomarkers as predictors of multiple sclerosis severity. *Mult Scler Relat Disord* 2025; 94: 106268.
5. International Multiple Sclerosis Genetics Consortium and MultipleMS Consortium. Locus for severity implicates CNS resilience in progression of multiple sclerosis. *Nature* 2023; 619(7969): 323–331.
6. Jokubaitis VG, Campagna MP, Ibrahim O, et al. Not all roads lead to the immune system: The genetic basis of multiple sclerosis severity. *Brain* 2023; 146(6): 2316–2331.
7. Calabrese M, Preziosa P, Scalfari A, et al. Determinants and biomarkers of progression independent of relapses in multiple sclerosis. *Ann Neurol* 2024; 96(1): 1–20.
8. Engelenburg HJ, van den Bosch AMR, Chen JQA, et al. Multiple sclerosis severity variant in DYSF-ZNF638 locus associates with neuronal loss and inflammation. *Iscience* 2025; 28: 108154.
9. Lublin FD, Reingold SC and Cohen JA. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology* 2014; 83(3): 278–286.
10. Kappos L, Wolinsky JS, Giovannoni G, et al. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed

disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. *JAMA Neurol* 2020; 77(9): 1132–1140.

11. Scalfari A, Traboulsee A, Oh J, et al. Smouldering-associated worsening in multiple sclerosis: An international consensus statement on definition, biology, clinical implications, and future directions. *Ann Neurol* 2024; 96(5): 826–845.
12. Correale J, Rush CA and Barboza A. Are highly active and aggressive multiple sclerosis the same entity. *Front Neurol* 2023; 14: 1132170.
13. Hardy TA, Tobin WO and Lucchinetti CF. Exploring the overlap between multiple sclerosis, tumefactive demyelination and Baló's concentric sclerosis. *Mult Scler* 2016; 22(8): 986–992.
14. Gholipour T, Healy B, Baruch NF, et al. Demographic and clinical characteristics of malignant multiple sclerosis. *Neurology* 2011; 76(23): 1996–2001.
15. Menon S, Zhu F, Shirani A, et al. Disability progression in aggressive multiple sclerosis. *Mult Scler* 2017; 23(4): 456–463.
16. Tintore M, Arrambide G, Otero-Romero S, et al. The long-term outcomes of CIS patients in the Barcelona inception cohort: Looking back to recognize aggressive MS. *Mult Scler* 2020; 26(13): 1658–1669.
17. Rush CA, MacLean HJ and Freedman MS. Aggressive multiple sclerosis: Proposed definition and treatment algorithm. *Nat Rev Neurol* 2015; 11(7): 379–389.
18. Scott TF, Laforet G and You X. Aggressive relapsing multiple sclerosis characterized by rapid disability progression. *Mult Scler Relat Disord* 2013; 2(4): 370–376.
19. Edan G, Comi G, Le Page E, et al. Mitoxantrone prior to interferon beta-1b in aggressive relapsing multiple sclerosis: A 3-year randomised trial. *J Neurol Neurosurg Psychiatry* 2011; 82(12): 1344–1350.
20. Saccardi R, Freedman MS, Sormani MP, et al. A prospective, randomized, controlled trial of autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: A position paper. *Mult Scler* 2012; 18(6): 825–834.
21. Bose G, Healy BC, Lokhande HA, et al. Early predictors of clinical and MRI outcomes using least absolute shrinkage and selection operator (LASSO) in multiple sclerosis. *Ann Neurol* 2022; 92(1): 87–96.
22. Gasperini C, Prosperini L, Rovira À, et al. Scoring the 10-year risk of ambulatory disability in multiple sclerosis: The RoAD score. *Eur J Neurol* 2021; 28(8): 2533–2542.
23. Brownlee WJ, Altmann DR, Prados F, et al. Early imaging predictors of long-term outcomes in relapse-onset multiple sclerosis. *Brain* 2019; 142(8): 2276–2287.
24. Monreal E, Fernández-Velasco JI, Álvarez-Lafuente R, et al. Serum biomarkers at disease onset for personalized therapy in multiple sclerosis. *Brain* 2024; 147(12): 4084–4093.
25. Schaller-Paule MA, Maiworm M, Schäfer JH, et al. Matching proposed clinical and MRI criteria of aggressive multiple sclerosis to serum and cerebrospinal fluid markers of neuroaxonal and glial injury. *J Neurol* 2024; 271(6): 3512–3526.
26. Lauerer M, Wiltgen T, Brückner C, et al. Predictors of early disability accumulation in newly diagnosed multiple sclerosis: Clinical, imaging and cerebrospinal fluid measures. *J Neurol Neurosurg Psychiatry* 17: 335037.
27. Iacobaeus E, Georgina A, Maria Pia A, et al. Aggressive multiple sclerosis (1): Towards a definition of the phenotype. *Mult Scler* 2020; 26(10): 1161–1169.
28. Arrambide G, Iacobaeus E, Amato MP, et al. Aggressive multiple sclerosis (2): Treatment. *Mult Scler* 2020; 26(10): 1170–1182.
29. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. *Neurology* 2018; 90(17): 777–788.
30. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult Scler* 2018; 24(2): 96–120.
31. Harding K, Williams O, Willis M, et al. Clinical outcomes of escalation vs early intensive disease-modifying therapy in patients with multiple sclerosis. *JAMA Neurol* 2019; 76(5): 536–541.
32. He A, Merkel B, Brown JWL, et al. Timing of high-efficacy therapy for multiple sclerosis: A retrospective observational cohort study. *Lancet Neurol* 2020; 19(4): 307–316.
33. Buron MD, Chalmer TA, Sellebjerg F, et al. Initial high-efficacy disease-modifying therapy in multiple sclerosis: A nationwide cohort study. *Neurology* 2020; 95(11): e1041–e1051.
34. Spelman T, Kalincik T, Zhang A, et al. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: Data from 2 different national strategies. *JAMA Neurol* 2021; 78(10): 1197–1204.
35. Iaffaldano P, Lucisano G, Caputo F, et al. Long-term disability trajectories in relapsing multiple sclerosis

patients treated with early intensive or escalation treatment strategies. *Ther Adv Neurol Disord* 2021; 14: 17562864211019574.

36. Brown JWL, Coles A, Horakova D, et al. Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA* 2019; 321(2): 175–187.
37. Uher T, Krasensky J, Malpas C, et al. Evolution of brain volume loss rates in early stages of multiple sclerosis. *Neurol Neuroimmunol Neuroinflamm* 2021; 8(3).
38. Giovannoni G, Lang S, Wolff R, et al. A systematic review and mixed treatment comparison of pharmaceutical interventions for multiple sclerosis. *Neurol Ther* 2020; 9(2): 359–374.
39. Goldschmidt C and McGinley MP. Advances in the treatment of multiple sclerosis. *Neurol Clin* 2021; 39(1): 21–33.
40. Samjoo IA, Worthington E, Drudge C, et al. Efficacy classification of modern therapies in multiple sclerosis. *J Comp Eff Res* 2021; 10(6): 495–507.
41. Scolding N, Barnes D, Cader S, et al. Association of British Neurologists: Revised (2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. *Pract Neurol* 2015; 15(4): 273–279.
42. Filippi M, Amato MP, Centonze D, et al. Early use of high-efficacy disease-modifying therapies makes the difference in people with multiple sclerosis: An expert opinion. *J Neurol* 2022; 269(10): 5382–5394.
43. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006; 354(9): 899–910.
44. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006; 354(9): 911–923.
45. Hutchinson M, Kappos L, Calabresi PA, et al. The efficacy of natalizumab in patients with relapsing multiple sclerosis: Subgroup analyses of AFFIRM and SENTINEL. *J Neurol* 2009; 256(3): 405–415.
46. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: A randomised controlled phase 3 trial. *Lancet* 2012; 380(9856): 1819–1828.
47. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: A randomised controlled phase 3 trial. *Lancet* 2012; 380(9856): 1829–1839.
48. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab more effective than interferon β-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012; 78(14): 1069–1078.
49. Ziemssen T, Bass AD, Berkovich R, et al. Efficacy and safety of alemtuzumab through 9 years of follow-up in patients with highly active disease: Post hoc analysis of CARE-MS I and II patients in the TOPAZ extension study. *CNS Drugs* 2020; 34(9): 973–988.
50. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* 2008; 358(7): 676–688.
51. Durozard P, Maarouf A, Boutiere C, et al. Efficacy of rituximab in refractory RRMS. *Mult Scler* 2019; 25(6): 828–836.
52. Hauser SL, Barr-Or A, Comi G, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017; 376(3): 221–234.
53. Turner B, Cree BAC, Kappos L, et al. Ocrelizumab efficacy in subgroups of patients with relapsing multiple sclerosis. *J Neurol* 2019; 266(5): 1182–1193.
54. Hauser SL, Barr-Or A, Cohen JA, et al. Ofatumumab versus teriflunomide in multiple sclerosis. *N Engl J Med* 2020; 383(6): 546–557.
55. Steinman L, Fox E, Hartung H-P, et al. Ublituximab versus teriflunomide in relapsing multiple sclerosis. *N Engl J Med* 2022; 387(8): 704–714.
56. Sharrack B, Saccardi R, Alexander T, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: Updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). *Bone Marrow Transplant* 2020; 55(2): 283–306.
57. Muraro PA, Mariottini A, Greco R, et al. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis and neuromyelitis optica spectrum disorder – recommendations from ECTRIMS and the EBMT. *Nat Rev Neurol* 2025; 21(3): 140–158.
58. Mariottini A, De Matteis E, Cencioni MT, et al. Haematopoietic stem cell transplantation for the treatment of multiple sclerosis: Recent advances. *Curr Neurol Neurosci Rep* 2023; 23(9): 507–520.
59. Brittain G, Coles AJ, Giovannoni G, et al. Autologous haematopoietic stem cell transplantation for immune-mediated neurological diseases: What, how, who and why. *Pract Neurol* 2023; 23(2): 139–145.
60. Boffa G, Inglese M and Mancardi GL. Hematopoietic stem cell transplantation for multiple sclerosis. In: Inglese M and Mancardi GL (eds)

Handbook of Clinical Neurology. Vol 202. New York: Elsevier, 2024, pp. 153–167.

61. Das J, Snowden JA, Burman J, et al. Autologous haematopoietic stem cell transplantation as a first-line disease-modifying therapy in patients with 'aggressive' multiple sclerosis. *Mult Scler* 2021; 27(8): 1198–1204.
62. Burt RK, Balabanov R, Burman J, et al. Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: A randomized clinical trial. *JAMA* 2019; 321(2): 165–174.
63. Boffa G, Lapucci C, Sbragia E, et al. Aggressive multiple sclerosis: A single-centre, real-world treatment experience with autologous haematopoietic stem cell transplantation and alemtuzumab. *Eur J Neurol* 2020; 27(10): 2047–2055.
64. Häußler V, Ufer F, Pöttgen J, et al. aHSCT is superior to alemtuzumab in maintaining NEDA and improving cognition in multiple sclerosis. *Ann Clin Transl Neurol* 2021; 8(6): 1269–1278.
65. Zhukovsky C, Sandgren S, Silfverberg T, et al. Autologous haematopoietic stem cell transplantation compared with alemtuzumab for relapsing-remitting multiple sclerosis: An observational study. *J Neurol Neurosurg Psychiatry* 2021; 92(2): 189–194.
66. Kalincik T, Sharmin S, Roos I, et al. Comparative effectiveness of autologous hematopoietic stem cell transplant vs fingolimod, natalizumab, and ocrelizumab in highly active relapsing-remitting multiple sclerosis. *JAMA Neurol* 2023; 80(7): 702–713.
67. Muraro PA, Zito A, Signori A, et al. Effectiveness of autologous hematopoietic stem cell transplantation versus alemtuzumab and ocrelizumab in relapsing multiple sclerosis: A single center cohort study. *Ann Neurol*. Published Online. doi:10.1002/ana.26730
68. Inglese M, Cohen JA, Sharrack B, et al. Chapter 20 – Ongoing randomized clinical trials on HSCT in multiple sclerosis. In: Inglese M and Mancardi GL (eds) *Handbook of Clinical Neurology*. Vol 202. New York: Elsevier, 2024, pp. 307–315.
69. Burt RK, Farge D, Saccardi R, et al. Autologous HSCT conditioning regimens for autoimmune diseases. In: Burt RK, Farge D, Ruiz MA, et al. (eds) *Hematopoietic Stem Cell Transplantation and Cellular Therapies for Autoimmune Diseases*. Boca Raton, FL: CRC Press, 2021, p. 204–212.
70. Burt RK, Farge D, Ruiz MA, et al. Late toxicity and supportive care of patients undergoing hematopoietic cell transplantation for autoimmune diseases. In: Burt RK, Farge D, Ruiz MA, et al. (eds) *Hematopoietic Stem Cell Transplantation and Cellular Therapies for Autoimmune Diseases*. Boca Raton, FL: CRC Press, 2021, p. 252–263.
71. Boffa G, Massacesi L, Inglese M, et al. Long-term clinical outcomes of hematopoietic stem cell transplantation in multiple sclerosis. *Neurology* 2021; 96: e1215–e1226.
72. Nicholas RS, Rhone EE, Mariottini A, et al. Autologous hematopoietic stem cell transplantation in active multiple sclerosis: A real-world case series. *Neurology* 2021; 97(9): e890–e901.
73. Silfverberg T, Zjukovskaja C, Ljungman P, et al. Haematopoietic stem cell transplantation for treatment of relapsing-remitting multiple sclerosis in Sweden: An observational cohort study. *J Neurol Neurosurg Psychiatry* 2024; 95: 125–133.
74. Burt RK, Cohen BA, Russell E, et al. Hematopoietic stem cell transplantation for progressive multiple sclerosis: Failure of a total body irradiation-based conditioning regimen to prevent disease progression in patients with high disability scores. *Blood* 2003; 102(7): 2373–2378.
75. Bowen JD, Kraft GH, Wundes A, et al. Autologous hematopoietic cell transplantation following high-dose immunosuppressive therapy for advanced multiple sclerosis: Long-term results. *Bone Marrow Transplant* 2012; 47(7): 946–951.
76. Samijn JP, te Boekhorst PA, Mondria T, et al. Intense T cell depletion followed by autologous bone marrow transplantation for severe multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2006; 77(1): 46–50.
77. Atkins HL, Bowman M, Allan D, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: A multicentre single-group phase 2 trial. *Lancet* 2016; 388(10044): 576–585.
78. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: Updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2012; 47(6): 770–790.
79. Monje ML, Mizumatsu S, Fike JR, et al. Irradiation induces neural precursor-cell dysfunction. *Nat Med* 2002; 8(9): 955–962.
80. Moore JJ, Massey JC, Ford CD, et al. Prospective phase II clinical trial of autologous haematopoietic stem cell transplant for treatment refractory multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2019; 90(5): 514–521.
81. Tolf A, Fagius J, Carlson K, et al. Sustained remission in multiple sclerosis after hematopoietic stem cell transplantation. *Acta Neurol Scand* 2019; 140(5): 320–327.

82. Nash RA, Hutton GJ, Racke MK, et al. High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. *Neurology* 2017; 88(9): 842–852.

83. Burman J, Iacobaeus E, Svenningsson A, et al. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: The Swedish experience. *J Neurol Neurosurg Psychiatry* 2014; 85(10): 1116–1121.

84. Mariottini A, Marchi L, Innocenti C, et al. Intermediate-intensity autologous hematopoietic stem cell transplantation reduces serum neurofilament light chains and brain atrophy in aggressive multiple sclerosis. *Front Neurol* 2022; 13: 820256.

85. Burt RK, Han X, Quigley K, et al. Real-world application of autologous hematopoietic stem cell transplantation in 507 patients with multiple sclerosis. *J Neurol* 2022; 269(5): 2513–2526.

86. Muraro PA, Martin R, Mancardi GL, et al. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. *Nat Rev Neurol* 2017; 13(7): 391–405.

87. Snowden JA, Badoglio M, Labopin M, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. *Blood Adv* 2017; 1(27): 2742–2755.

88. Alexander T and Greco R. Hematopoietic stem cell transplantation and cellular therapies for autoimmune diseases: Overview and future considerations from the Autoimmune Diseases Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant* 2022; 57(7): 1055–1062.

89. Saccardi R. The 50th annual meeting of the European society for blood and marrow transplantation: Physicians – oral session (O009-O154). *Bone Marrow Transplant* 2024; 59(Suppl. 1): 20–139.

90. Silfverberg T, Zjukovskaja C, Noui Y, et al. BEAM or cyclophosphamide in autologous haematopoietic stem cell transplantation for relapsing-remitting multiple sclerosis. *Bone Marrow Transplant* 2024; 59(8): 1601–1610.

91. Curro' D, Vuolo L, Gualandi F, et al. Low intensity lympho-ablative regimen followed by autologous hematopoietic stem cell transplantation in severe forms of multiple sclerosis: A MRI-based clinical study. *Mult Scler* 2015; 21(11): 1423–1430.

92. Peffault de Latour R, Risitano A and Dufour C. Severe aplastic anemia and PNH. In: Carreras E, Dufour C, Mohty M, et al. (eds) *The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies*. New York: Springer, 2019, pp. 579–585.

93. Visweswaran M, Hendrawan K, Massey JC, et al. Sustained immunotolerance in multiple sclerosis after stem cell transplant. *Ann Clin Transl Neurol* 2022; 9(2): 206–220.

94. Hendrawan K, Khoo MLM, Visweswaran M, et al. Long-term suppression of circulating proinflammatory cytokines in multiple sclerosis patients following autologous haematopoietic stem cell transplantation. *Front Immunol* 2021; 12: 782935.

95. Massey J, Visweswaran M, Khoo M, et al. Detailed immunophenotyping of the hematopoietic graft from patients with multiple sclerosis undergoing autologous hematopoietic stem cell transplant. *Cytotherapy* 2023; 25(12): 1271–1276.

96. Massey J, Jackson K, Singh M, et al. Haematopoietic stem cell transplantation results in extensive remodelling of the clonal T cell repertoire in multiple sclerosis. *Front Immunol* 2022; 13: 798300.

97. Hamerschlak N, Rodrigues M, Moraes DA, et al. Brazilian experience with two conditioning regimens in patients with multiple sclerosis: BEAM/horse ATG and CY/rabbit ATG. *Bone Marrow Transplant* 2010; 45(2): 239–248.

98. Burt RK, Farge D, Ruiz MA, et al. Early toxicity and supportive care of HSCT for autoimmune diseases. In: Burt RK, Farge D, Ruiz MA, et al. (eds) *Hematopoietic Stem Cell Transplantation and Cellular Therapies for Autoimmune Diseases*. Boca Raton, FL: CRC Press, 2021, pp. 241–251.

99. Roberts F, Hobbs H, Jessop H, et al. Rehabilitation before and after autologous haematopoietic stem cell transplantation for patients with multiple sclerosis: Consensus guidelines and recommendations. *Front Neurol* 2020; 11: 556141.

100. Burt RK, Muraro PA, Farge D, et al. New autoimmune diseases after autologous hematopoietic stem cell transplantation for multiple sclerosis. *Bone Marrow Transplant* 2021; 56(7): 1509–1517.

101. Alping P, Burman J, Lycke J, et al. Safety of alemtuzumab and autologous hematopoietic stem cell transplantation compared to noninduction therapies for multiple sclerosis. *Neurology* 2021; 96(15): e1574–e1584.

102. Lee H, Nakamura K, Narayanan S, et al. Impact of immunoablation and autologous hematopoietic stem cell transplantation on gray and white matter atrophy in multiple sclerosis. *Mult Scler* 2018; 24(8): 1055–1066.

103. Roccatagliata L, Rocca M, Valsasina P, et al. The long-term effect of AHSCT on MRI measures of MS evolution: A five-year follow-up study. *Mult Scler* 2007; 13(8): 1068–1070.

104. Kvistad SAS, Lehmann AK, Trovik LH, et al. Safety and efficacy of autologous hematopoietic stem cell transplantation for multiple sclerosis in Norway. *Mult Scler* 2020; 26(14): 1889–1897.

105. Chatterton S, Withers B, Sutton IJ, et al. Pregnancy post autologous stem cell transplant with BEAM conditioning for multiple sclerosis. *Mult Scler* 2021; 27(13): 2112–2115.

106. Massarotti C, Sbragia E, Boffa G, et al. Menstrual cycle resumption and female fertility after autologous hematopoietic stem cell transplantation for multiple sclerosis. *Mult Scler* 2021; 27(13): 2103–2107.

107. Salooja N, Szydlo RM, Socie G, et al. Pregnancy outcomes after peripheral blood or bone marrow transplantation: A retrospective survey. *Lancet* 2001; 358(9278): 271–276.

108. Loren AW, Chow E, Jacobsohn DA, et al. Pregnancy after hematopoietic cell transplantation: A report from the late effects working committee of the CIBMTR. *Biol Blood Marrow Transplant* 2011; 17(2): 157–166.

109. Muraro PA, Pasquini M, Atkins HL, et al. Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. *JAMA Neurol* 2017; 74(4): 459–469.

110. Mehra V, Rhone E, Widya S, et al. Epstein-Barr virus and monoclonal gammopathy of clinical significance in autologous stem cell transplantation for multiple sclerosis. *Clin Infect Dis* 2019; 69(10): 1757–1763.

111. Saccardi R. The 48th annual meeting of the European society for blood and marrow transplantation: Physicians – oral sessions (O009–O155). *Bone Marrow Transplant* 2022; 57(Suppl1): 16–99.

112. Shi K, Li H, Chang T, et al. Bone marrow hematopoiesis drives multiple sclerosis progression. *Cell* 2022; 185(13): 2234–2247; e17.

113. Mariottini A, Muraro PA and Saccardi R. Should autologous hematopoietic stem cell transplantation be offered as a first-line disease modifying therapy to patients with multiple sclerosis. *Mult Scler Relat Disord* 2023; 78: 104932.