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Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis and neuromyelitis optica spectrum disorder — recommendations from ECTRIMS and the EBMT

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Dedication

We wish to dedicate this article to the memory of Riccardo Saccardi, who passed away on 19th February 2024 after a long battle with cancer. His relentless commitment to advancing the application of haematopoietic stem cell transplantation in autoimmune diseases will

continue to influence our work for many years to come. Together with his knowledge, his kindness and humility made him a uniquely collaborative individual, and we and his many other friends and colleagues will deeply miss him.

Abstract **|** Autologous haematopoietic stem cell transplantation (AHSCT) is a treatment option for patients with relapsing forms of multiple sclerosis (MS) that are refractory to disease-modifying therapy (DMT). AHSCT after failure of high-efficacy DMT in aggressive forms of relapsing–remitting (RR)MS is a generally accepted indication, yet the optimal placement of this approach in the treatment sequence is not universally agreed upon. Uncertainties also remain with respect to other indications, such as in rapidly evolving, severe, treatment-naive MS, progressive MS, and neuromyelitis optica spectrum disorder (NMOSD). Furthermore, treatment and monitoring protocols, rehabilitation and other supportive care before and after AHSCT need to be optimized. To address these issues, we convened a European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Focused Workshop in partnership with the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP), in which evidence and key questions were presented and discussed by experts in these diseases and in AHSCT. Based on the workshop output and subsequent written interactions, this Consensus statement provides practical guidance and recommendations on the use of AHSCT in MS and NMOSD. Recommendations are based on the available evidence, or on consensus when evidence was insufficient. We summarize the key evidence, report the final recommendations, and identify areas for further research.

[H1] Introduction

Haematopoietic stem cell transplantation (HSCT) is a haematological procedure that has increasingly been used since the late 1990s for the treatment of autoimmune diseases that are refractory to conventional disease-modifying treatment (DMT) [1,2]. HSCT encompasses two procedures: autologous HSCT (AHSCT), in which the haematopoietic stem cells (HSCs) used are the patient's own, or allogeneic HSCT, in which the HSCs derive from a healthy donor. The most common neurological indication for AHSCT is multiple sclerosis (MS), an immune-mediated demyelinating and degenerative disease of the CNS that can cause irreversible disability[3]. Much less frequently, HSCT — in a few cases allogeneic HSCT — has also been used to treat other neuroinflammatory diseases, such as neuromyelitis optica spectrum disorders (NMOSD)[4].

AHSCT is highly effective at stopping inflammation in the brain, demonstrated by suppression of clinical and MRI-detected MS disease activity[5]. It can also stabilize or even improve function in relapsing–remitting MS, though the benefits are less clear in primary progressive MS and secondary progressive MS[6]. Though the safety profile of AHSCT has improved markedly over time[7], the treatment involves higher acute risk than many approved DMTs for MS, so the optimal placement of AHSCT in the therapeutic algorithm for MS remains uncertain. Key questions include the criteria for patient selection, the choice of treatment protocol, the management of rehabilitation, fertility and vaccinations, and the use of DMTs after AHSCT. Long-term monitoring of adverse events and neurological outcomes all require further investigation.

In this Consensus statement, the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Society for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP) review current knowledge and provide recommendations for the use of AHSCT in adults with MS or NMOSD, including its indication and positioning in the treatment algorithm, candidate selection, transplant methodology and patient management. The use of HSCT in the paediatric setting was not covered; specific recommendations are provided elsewhere by the EBMT ADWP and Paediatric Diseases Working Party (PDWP)[8].

[H1] Methods

[H2] Focused workshop

An ECTRIMS Focused Workshop to discuss use of AHSCT for the treatment of MS and other disorders was organized by ECTRIMS in partnership with the EBMT ADWP under the

leadership of the Organizing Committee (P.A.M., R.G., J.B., E.I., M.I., J.A.S., B. Stankoff and B.Sharrack and was held as a 2-day digital event in March 2022. The aims of the workshop were: to produce practical guidance for clinicians, patients and healthcare payers on the basis of expert consensus recommendations with the support of the leading sub-specialist organizations; to provide a forum for the professional and scientific development of participants who, as established or emerging leaders in the neurological and haematological communities across Europe, could subsequently share their knowledge in their respective countries and further afield; and to disseminate the results with published articles and societal media with high potential to influence and improve clinical practice and healthcare policy development.

As customary for ECTRIMS Focused Workshops, participation was by invitation; participants were nominated by the Organizing Committee to balance optimal expertise with equality of gender, a broad geographic distribution within Europe, and adequate societal representation from the subspecialist associations, ECTRIMS and the EBMT ADWP. The previous and current Presidents of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS; J.C. and M.F.F., respectively) were also invited to represent ACTRIMS. The workshop included two plenary sessions and four parallel sessions, divided into neurological and haematological streams. Twenty speakers presented the current evidence and identified key questions on the use of HSCT in MS and NMOSD, and each session was followed by round-table discussions that involved all speakers and named key discussants. Workshop chairs presented summaries of the parallel sessions and discussions to all attendees. On the basis of the agreed output, two members of the Organizing Committee (P.A.M. and B. Sharrack) led the generation of a consensus summary. The scientific programme, recorded sessions and a highlights document from the workshop are publicly available on the ECTRIMS website[9].

[H2] Preparation of the Consensus statement

After the workshop, the Organizing Committee held a de-briefing meeting in which a manuscript writing plan was agreed to develop the third workshop aim. A manuscript outline including the structure and key points from the workshop was prepared by P.A.M. and B. Sharrack, circulated for comments and agreed upon within the Organizing Committee. The outline was developed into a full manuscript draft by P.A.M. and A.M. by adding detailed information and output from workshop slide decks, presentation recordings, session summaries and consensus summary. All authors reviewed the initial draft and contributed to

subsequent drafts via email correspondence. During this revision process, the manuscript was updated and enriched with information obtained through structured searches to include relevant literature published up to the end of June 2024. Recommendations are based on scientific evidence from primary research, systematic reviews and meta-analyses wherever possible, and rely on consensus opinion only when the evidence was limited or unavailable. Consensus was reached through revision of the draft to address comments from all co-authors until agreement was reached. Three rounds of revision were required to establish consensus.

[H2] Stakeholders

Stakeholders interested in this Consensus statement include people with MS or NMOSD, their families, carers and any other affected individuals; MS and NMOSD healthcare professionals, including physicians, nurses, pharmacists, physician assistants, technologists, physical therapists, rehabilitation therapists, psychologists and allied professionals; researchers in neurological disease, including neuroscientists and neuro-immunologists; neurological and neuroinflammatory diseases healthcare payers, insurers, commissioners and public health organizations; and MS and NMOSD patient associations and scientific societies. Representatives of all stakeholders were not included in the workshop owing to logistical limitations.

[H1] Rationale and immunological mechanisms of AHSCT

[H2]

Immune reconstitution

The pathogenesis of MS is initiated by unfavourable interactions between genetic and environmental risk factors[1] that lead, via poorly understood mechanisms, to the activation and migration of pro-inflammatory B cells and T cells into the CNS[10]. The rationale for the use of AHSCT in MS and other diseases is that this treatment eradicates disease-associated adaptive and innate immune components, followed by restoration of immune tolerance through deep reconstitution of the immune system, leading to long-term suppression of new focal inflammatory activity[11]. After ablation of the haemato–lymphoid system with high-dose chemotherapy, immunological recovery usually occurs within 6 months for $CD19^+$ B cells, $CD8^+$ T cells and natural killer cells, but requires up to 2 years for $CD4^+$ naive T cells and central memory T cells[12-15].

Early immune reconstitution is promoted by peripheral expansion of cells that survive lympho–ablative conditioning. During later reconstitution (>1 year after AHSCT), new naive T cells are generated by de novo maturation in a reactivated thymus. This process is indicated by a gradual increase in markers of recent thymic emigrants (CD31 and T cell receptor excision circles) in the peripheral blood, and extensive renewal, i.e. ablation of pre-treatment T lymphocytes followed by replacement with new ones, as demonstrated by extensive changes [of the T cell receptor (TCR) in the peripheral blood[13,15-19] and the cerebrospinal fluid (CSF)[18,19].

[H2] Mechanisms of disease suppression

Changes in the immune system that have been described after AHSCT in MS include an increase in regulatory cell phenotypes (such as FoxP3$^+$ T regulatory (T_{reg}) cells), reduced T helper (T_H) 17 cell responses[20,21], and changes in cytokine patterns and immune cell gene expression that characterize a more tolerogenic environment[15,22-24]. Re-emergence of myelin basic protein (MBP, one of the CNS myelin components) reactive cells after AHSCT has been reported, but subsequent data suggest that T cell reactivity to MS-related antigens, tested with a broad panel of peptide pools covering not only the myelin proteins MBP, myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP) but also the nonmyelin MS autoantigens RASGRP2 and GDPLFS and further including peptides covering the MS-related environmental agent EBV and its latency-associated protein EBNA1, a few additional EBV peptides and peptides from cytomegalovirus (CMV) and influenza virus (CEFII), yielded individually heterogeneous results, with overall decreased specificity for MS autoantigens in CD4+ effector memory (EM) T cells after AHSCT, whereas reactivity toward EBV increased, more pronounced in patients with EBV reactivation[15].

Levels of switched memory B cells are reduced after AHSCT suggesting the ablation of immunoglobulin-producing B cells that may take part in autoimmune processes and the B cell receptor (BCR) repertoire is less diverse early after treatment but renewed at later stages[25]. Reductions in levels of mucosal associated invariant T (MAIT) cells with inflammatory phenotypes and increases in CD56^{high} natural killer cells, a subset of cells with immune regulatory functions have also been reported after AHSCT[26-28]. No data are currently available on the effects of AHSCT on the microglial compartment in vivo; microglia might not be renewed given that they are tissue-resident and slow cycling, but changes in phenotype and states of activation are possible.

In addition to these mechanisms, the effects of allogeneic HSCT might involve replacement of autoreactive cells by healthy allogeneic cells and the development of graft-versus-autoimmunity effect[29]. However, the allogeneic procedure carries higher risks of morbidity from graft-versus-host disease and mortality that curtail its utilisation in autoimmune diseases, except as developmental (i.e. investigative) indication in a prospective clinical study[30].

[H2] Immunological and other biomarker research and biobanking

Investigational immune monitoring after AHSCT can be done with use of different techniques, including flow cytometry[13], gene expression analyses[24], mass cytometry[31], deep sequencing of TCRs[18], and single-cell RNA sequencing[32]. Monitoring of neurofilament light chain and glial fibrillary acidic protein levels could provide insights into the effects of AHSCT on neuronal and glial pathology, similar to the expanding use of these biomarkers in clinical trials and monitoring effects of DMT in patient cohorts. Further studies with novel biomarkers are needed to understand the effects of AHSCT on microglia and astroglia activation, on smouldering inflammation in the meninges and/or brain parenchyma, and on brain remyelination and other forms of functional regeneration and repair. Collection and storage of biological specimens for biobanking could contribute to routine supportive care and is recognised as essential to enable further investigation of the biological effects and mechanisms of action of AHSCT in autoimmune disease. The EBMT Autoimmune Diseases and Immunobiology Working Parties have published recommendations for biobanking of samples and laboratory immune monitoring in patients with autoimmune disease undergoing AHSCT[33].

[H2] Recommendations

- Include objectives in clinical trials and structured treatment programmes that will provide insight into the mechanisms of AHSCT.
- Offer informed consent for participation in mechanistic research to people who are enrolled in clinical trials or other ethically approved clinical studies or case series.
- Plan to collect blood for studies of immune reconstitution and mechanisms of action before and after AHSCT at defined timepoints (for example, quarterly during the first year, then yearly) and at any relapses[33].

- Consider studying CSF biomarkers of inflammation, neuro-axonal injury and glial injury to inform prediction and assessment of treatment response.
- Follow the relevant specialist guidelines for immune monitoring and biobanking[33].
- Harmonize sample handling and processing across sites to enable pooling of samples for multicentre collaborations.

[H1] Clinical evidence on AHSCT in MS

[H2] Case series and cohort studies

Several case series, cohort studies and prospective single-arm trials of AHSCT for MS have been published, in which different protocols have been used and patient populations have been heterogeneous[34]. Since the earliest studies, when AHSCT was almost exclusively used to treat people with progressive and advanced MS[35,36], the selection criteria have evolved considerably. AHSCT has increasingly been used to treat relapsing–remitting MS rather than progressive forms of MS, and these developments in patient selection, along with accumulated experience at transplant centres, have improved safety[5]. For this reason, we focused on evidence from contemporary practice by searching the literature and reviewing studies that met the following criteria: at least 10 individuals were treated with AHSCT; published in the past 5 years (1st January 2019–5th July 2024; listed in PubMed; written in the English language; reported objective neurological outcomes, including progression-free survival or no evidence of disease activity (NEDA); and reported transplant-related mortality. Publications that provided information obtained from self-reported questionnaires or remote interviews were not considered as evidence for our consensus and recommendations.

We identified 26 publications that met the criteria, most of which reported retrospective, single-centre or multi-centre studies. Amongst these, we identified 17 studies that involved a single treatment group that underwent AHSCT (Supplementary table 1)[14,37-53]. In nine studies, AHSCT was compared with other therapies in two or more treatment groups (Supplementary table 2)[49,54-61]. Half of the 26 studies included only people with relapsing–remitting MS. As expected, the cohorts in these studies had lower average EDSS scores at baseline than the cohorts that included people with progressive MS, and their outcomes were better, with high rates of progression-free survival (80–100%) and NEDA (70–80%) (Supplementary table 1). The average age of participants in these 26 studies ranged from 27 years to 44 years, reflecting appropriate age windows. In three studies in which people

aged <45 years with relapsing–remitting MS, a short duration of disease (5 years or less from diagnosis) and recent inflammatory activity were treated with AHSCT, near-complete progression-free survival and improvement of disability was observed[37,38,42]; in one study, AHSCT was used as a first-line disease-modifying therapy[42]. Similar outcomes were observed in previous studies of AHSCT in people with relapsing–remitting MS[62,63].

Given that long-term outcomes in MS are of particular importance, we also considered key evidence published before 2019. Long-term outcomes in a large cohort that were treated with AHSCT for MS were first reported in a retrospective joint analysis of the EBMT and the Centre for International Blood and Marrow Transplant Research (CIBMTR) databases that included 281 patients with a median follow-up period of 6.6 years[64]. The large majority had progressive forms of MS (78%) and only 16% had relapsing–remitting MS. Overall progression-free survival at 5 years was 46%, but progression-free survival was considerably higher in the relapsing–remitting MS subgroup (73%, 95% CI 57–88%) than the progressive MS subgroup (33%, 95% CI 24–42%). Transplant-related mortality was high at 2.8%, explained by the large proportion of people with advanced-stage progressive MS[64]. In a subsequent cohort of 210 people with MS (58% with relapsing–remitting MS) reported by the Italian BMT-MS Study Group, the overall outcomes were better than in the earlier study — the overall progression-free survival was 65% at 10 years after AHSCT, the progression-free survival was higher in relapsing–remitting MS compared to progressive MS (71% vs 57%), and the transplant-related mortality was 1.4%[44]. Most recently, sustained complete remission of MS has been demonstrated in two Swedish case series that included only people with relapsing–remitting MS who were followed up for up to 10 years after AHSCT[37,51]. Progression-free survival was 87% at 10 years, and there was no transplant-related mortality[51].

The nine studies in which AHSCT was compared with standard DMTs (Supplementary table 2) were all retrospective, non-randomized and/or non-blinded, six were single-centre studies and three were multi-centre studies (Supplementary table 2). The most frequently used conditioning regimens were carmustine (BCNU), etoposide, cytosine arabinoside (Ara-C) and melphalan (BEAM) with anti-thymocyte globulin (ATG; BEAM–ATG) or cyclophosphamide–ATG (Supplementary table 2), and the most common comparator was alemtuzumab, which was used in five studies. Baseline characteristics of participants were highly variable across the studies; some included only people with relapsing–remitting MS, others included only people with secondary progressive or primary progressive MS, and others included a mixture. Average age, disease duration and baseline

EDSS score were also variable (Supplementary table 2). All five studies in which AHSCT was compared with alemtuzumab showed that AHSCT had a superior effect on relapses, NEDA and MRI activity[54-58]. AHSCT was also superior to alemtuzumab in its effects on disability progression in two studies[54,57], though disability outcomes were similar in the other three studies[55,56,58]. This discrepancy could be explained by study limitations, including relatively short observation periods and the heterogeneity of the patient populations and the assessments.

In two multicentre retrospective studies, data were collected from several centres across several countries to enable propensity-score matched cohort comparisons[60,61]. One of these studies showed that AHSCT in highly active relapsing–remitting MS was considerably superior to fingolimod and marginally superior to natalizumab in relation to relapse-based and disability-based outcomes, but was not superior to ocrelizumab over a short duration of follow-up[61]. In the other study, treatment of primary progressive MS and secondary progressive MS with AHSCT was compared with treatment with natalizumab[59]. The ASCEND trial had previously demonstrated that natalizumab was ineffective in progressive MS[65], and the comparison identified no difference in outcomes, leading to the conclusion that AHSCT is similarly ineffective[60]. While providing valuable information, both studies have several limitations: a reliance on statistical methods to match patients who were selected, treated and followed up in different centres with heterogenous criteria, treatment protocols and assessments; small numbers of individuals in the matched groups, particularly in the study of progressive MS[60] and in the group that received ocrelizumab[61]; high dropout rates and short durations of follow-up, particularly for the group that received ocrelizumab (mean 1.52 years vs 3.78 years for the AHSCT matched cohort) [61]; and a lack of MRI data[60,61]. The remaining two of the nine comparative studies report results in patients with SPMS[49,59] and they are discussed in the following section on AHSCT in progressive forms of MS. No transplant-related mortality was reported in most (7 of 9) of the comparative studies (Supplementary table 2).

[H2] AHSCT in progressive forms of MS

Most studies of AHSCT in progressive MS were performed during the early 2000s[39,49,66-71] so are not included in the studies that met our search criteria (Supplementary tables 1 and 2). Outcomes of these studies were widely variable — progression-free survival ranged from 36% at 3 years[72] to 77% at 5 years after AHSCT[73]. Such variability could be explained, at least in part, by heterogeneity in the patient populations, the definitions of MS progression

and treatment failure that were used; and in the conditioning regimens used. Overall, outcomes were worse when total body irradiation protocols were used, possibly owing to a direct neurotoxic effect[74-76].

In large cohort studies of AHSCT in secondary progressive MS, progression-free survival at 5 years ranged from 33%[64] to 71%[44], but the lack of a control group makes it impossible to establish whether these rates signify any reduction in disability progression. Retrospective matched studies in which AHSCT was compared with available treatments suggested some benefit in this respect in some individuals[39,49]. In a small study comparing outcomes in patients with secondary progressive MS treated with AHSCT utilising the BEAM–ATG protocol (n=31) or cyclophosphamide (n=62), the two groups showed similar worsening of disability over a mean follow up >90 months but in a Cox regression analysis there was a trend to better progression-free survival in AHSCT compared to Cy (hazard ratio [HR] = 0.65, 95% confidence interval = 0.28–1.52, p = 0.320), equivalent to a 35% reduction in the risk of progression, non-significant probably because of insufficient power of this study for this outcome measure. [59] AHSCT was superior for suppression of relapses[59]. A registry-based study has indicated that AHSCT (BEAM–ATG protocol in most instances) in active secondary progressive MS significantly slowed disability progression and increased the likelihood of sustained disability improvement when compared with standard immunotherapy[49]. As mentioned above, comparison of AHSCT and natalizumab for primary progressive and secondary progressive MS identified no differences in MS relapse or disability outcomes[60] (Supplementary table 2).

Some evidence suggests that AHSCT affects the pathogenic mechanisms that underlie progressive disease. Specifically, AHSCT reduced brain atrophy rates in a subset of individuals with secondary progressive MS[39,77], and levels of serum neurofilament light chain (NfL) after AHSCT were similar to those in relapsing–remitting MS[47,78]. Levels of NfL in the CSF might be a more sensitive measure than that in the serum, and data from people with relapsing–remitting MS show a significant reduction in these levels after AHSCT that lasted for the duration of the 5-year follow-up[50]. Comparisons of AHSCT with other treatments in primary progressive MS are limited, but suggest similar effects on disability outcomes as seen in secondary progressive MS, though the benefit seems to be smaller[64,79].

[H2] Randomized clinical trials

Only two randomized clinical trials (RCTs) of AHSCT have been published[80,81]. The first, known as the ASTIMS trial, was terminated early owing to slow accrual of participants, and

the primary endpoint was changed from confirmed EDSS progression to the cumulative number of new T2 MRI lesions over a 4-year period. When the study was closed, it included 21 people with MS (33% relapsing–remitting MS) who were randomly assigned to receive either AHSCT with the BEAM–ATG protocol, or mitoxantrone[80]. On the basis of the MRI outcomes, AHSCT was superior to mitoxantrone (79% reduction in the number of new T2 lesions and relapse activity), but no significant difference was apparent in disability progression (57% for AHSCT versus 48% for mitoxantrone). In the second trial, known as the MIST trial, 110 people with relapsing–remitting MS were randomly assigned to receive either AHSCT with the cyclophosphamide–ATG protocol or DMTs that were approved by the FDA, excluding alemtuzumab[81]. Over a median follow-up of 2 years, AHSCT was superior to DMTs with respect to the primary outcome of progression-free survival at year 5 (90% versus 25%), and with respect to relapse-free survival at year 5 (85% versus 15%) and NEDA-3 at year 5 in a post-hoc analysis (78% versus 3%). One limitation of this study is that only 53% of the control group received high-efficacy DMTs (natalizumab or mitoxantrone) and the remainder of this group received moderate-efficacy DMTs. Ongoing [RCTs have been designed to overcome this limitation by including individuals receiving all current high-efficacy DMTs, including alemtuzumab, ocrelizumab, ofatumumab and cladribine in addition to natalizumab and mitoxantrone (see Investigative indications in relapsing–remitting MS).

[H2] Meta-analyses

A meta-analysis published in 2017 highlighted the importance of AHSCT protocol refinement and selection of patients for optimizing safety and efficacy outcomes in MS[7]. The study included 764 people from 15 studies (including one RCT) published between 1995 and 2016, in which various conditioning regimens were used[7]. Transplant-related mortality markedly decreased over time — among 349 individuals who underwent AHSCT after 2005, transplant-related mortality was 0.3%, compared with 3.6% among 415 individuals who underwent AHSCT before 2005. The higher transplant-related mortality in the older studies was associated with a lower proportion of people with relapsing–remitting MS and a higher EDSS score at baseline among those treated. AHSCT was associated with long-term suppression of new focal inflammatory activity (clinical relapses and new T2 and gadolinium-enhancing lesions on MRI) in individuals who underwent AHSCT, but the effect on EDSS progression was highly heterogeneous across studies and mostly depended on the proportion of participants with progressive forms of MS[7]. Pooled rates of EDSS progression were 17.1% at 2 years and 23.3% at 5 years, and lower 2-year progression rates were

associated with inclusion of a higher proportion of people with relapsing–remitting MS[7]. The pooled proportion of NEDA (which was reported in five studies) at years two and five was 83% (range 70–92%) and 67% (range 59–70%), respectively. Indirect comparisons of NEDA outcomes with AHSCT and DMTs suggest that AHSCT could be more effective in selected individuals, although comparative data from RCTs are needed to determine whether this is the case[5,82].

In a later meta-analysis that included 4,831 people with MS from 50 studies, the pooled estimates of progression-free survival and relapse-free survival were 73% (95% CI 69–77%) and 81% (95% CI 76–86%), respectively. The pooled proportion of people with MS in whom NEDA was maintained was 68% (95% CI 59–77%), and transplant-related mortality was 4.0% (95% CI 2–6%)[83], but this overall rate is strongly influenced by high transplant-related mortality in older studies[7]. Taken together, the meta-analyses are useful to illustrate the evolution of the field, but their pooled estimates are influenced by historical practice and the heterogeneity of patient populations, treatment protocols and centres across studies, limiting conclusions that can be drawn about safety and efficacy.

[H2] Patient-reported outcomes and narrative studies

Patient-reported outcomes (PROs) on quality of life (QoL) have not been systematically included in observational studies of AHSCT. However, PROs assessed with health-related QoL measures, including the Multiple Sclerosis Impact Scale (MSIS-29) and Short Form 36 (SF-36) scores, have been reported in some studies, usually as secondary outcomes[62,63], and investigated more fully in two studies[84,85]. Improvements in health-related QoL have consistently been associated with sustained clinical stabilization. Physical and psycho-social health perceptions of people with MS who had undergone AHSCT have also been investigated in qualitative studies of lived experiences through the various phases of AHSCT[86-88]. Important findings from these studies are that AHSCT was described by many participants as a second chance and an opportunity for a new life, enabling a transition from a state of illness to a state of health and countering a previous profound uncertainty [86]. Moreover, AHSCT was seen as a life-changing event
accompanied by both psychological and physical stress but accompanied or followed by a feeling of regaining control and a lasting positive effect[87]. Patients had high expectations about AHSCT but felt that they did not have enough information available to consider it[88], and those who already had the treatment wished they could have been provided information and access to this treatment option earlier in their MS course[87]. Implementation of PROs in

clinical trials and clinical practice has recently been recommended by the Autoimmune Diseases Working Party, Nurses Group, and Patient Advocacy Committee of the EBMT to capture patient perspectives and evaluate how they are affected by AHSCT[89].

[H2] Recommendations

- Continue to collect evidence from real-world cohorts who have undergone AHSCT and report baseline and follow-up clinical data and MRI data (acquired with a standardized protocol whenever possible[90]) to the EBMT database (or the appropriate extra-European organization) to facilitate clinical research.
- Collect PROs and QoL measures in cohorts and trials where possible.
- Share and disseminate evidence with patients, health practitioners and healthcare providers and payers.
- Consider offering participation in approved clinical trials and observational studies to all eligible patients; RCTs are particularly encouraged.
- Improve participant retention and collection of long-term data from all treated individuals, as these factors are especially important to avoid biases.
- Harmonize the endpoints and data collection methodology in cohort studies and RCTs to enable future meta-analyses.

[H1] Indications for AHSCT in MS

[H2] Relapsing–remitting MS

[H3] Established indications and placement in the treatment sequence

AHSCT has been endorsed as a standard of care for the treatment of relapsing–remitting MS that is refractory to conventional DMTs by the EBMT[2,30], the American Society for Blood and Marrow Transplantation[91], the US National MS Society[92] and the Brazilian Society of Bone Marrow Transplantation[93]. Compelling evidence of the need to target inflammation early in the disease course prompted a shift from stepped care to early escalation and induction strategies, as recommended by the European Academy of Neurology (EAN)–ECTRIMS guidelines on the treatment of MS[94]. High-efficacy DMTs (usually including the monoclonal antibodies alemtuzumab, natalizumab, ocrelizumab and ofatumumab[95] and, in some classifications, cladribine[96]) are more effective when treatment is initiated early[97-101]. Given that AHSCT is generally more effective than DMTs and that treatment at a younger

age and after a lower number of previous DMTs is associated with lower rates of long-term progression[64], its early use in people with highly active or aggressive MS that is not responding to high-efficacy DMTs could be beneficial.

The general principles of evaluating suitability for AHSCT are widely accepted (Figure 1). We also provide patient selection recommendations with more specifications (Box 1). Regarding prior exposure to DMTs, AHSCT is indicated for individuals with relapsing–remitting MS and markers of aggressive disease after failure of any one high-efficacy DMT. In treatment-naive individuals, we recommend that AHSCT is considered only for those with rapidly evolving, severe MS with poor prognostic factors. However, the optimal placement of AHSCT in the treatment sequence for MS remains challenging for several reasons, including a lack of consensus on the definition of "highly active or aggressive MS" (estimated as 4–14% of cases)[102]. While many factors are known to be associated to aggressive MS forms, including clinical features such as high frequency of relapses and rapid accumulation of neurological dysfunction, MRI findings, neuropathological findings, immunological features in the blood, biomarker correlates and genetic markers, the retrospective nature of the assessment in most definitions, and high uncertainty in the prediction of disease outcomes in any given individual precluded achieving a consensus in the 2018 ECTRIMS Focused Workshop on aggressive MS [103]. Eligibility criteria are also likely to change over time owing to the rapid evolution of the therapeutic scenario and clinical evidence.

[H3] Investigative indications

Four RCTs are ongoing to compare AHSCT with high-efficacy DMTs (Table 1): RAM-MS[104], STAR-MS[105], BEAT-MS[106] and NET-MS[107]. Though the inclusion criteria and transplantation protocols differ, these trials have several similarities in design, including a requirement for prior treatment failure (with limited exceptions in STAR-MS), a focus on relapsing–remitting MS, and the use of NEDA as the primary outcome, except in BEAT-MS in which the primary endpoint is relapses. As comparator DMTs, alemtuzumab and ocrelizumab are available options in all the RCTs; other high-efficacy DMTs (natalizumab, cladribine and other anti-CD20 monoclonal antibodies) are variably allowed. Secondary outcome measures vary, and include MRI, visual function, cognition, disability worsening and improvement, fatigue, depression, quality of life, and economic analysis. Blood and CSF biomarkers and mechanistic studies are also coordinated with the protocols. The results of

these RCTs, which are expected in 3–5 years, should inform us about the effectiveness of AHSCT in comparison with high-efficacy DMTs.

People with a very aggressive presentation of MS and poor prognostic factors can be considered for AHSCT as an investigative treatment option even without prior treatment failure[105]. In this context, the individual's risk-to-benefit profile should be accurately evaluated in a highly specialized multidisciplinary setting. As the window of therapeutic opportunity is narrower for these individuals, AHSCT as a first-line treatment could be beneficial. Indeed, in a retrospective study that included 20 people with aggressive relapsing–remitting MS with moderate to severe disability at baseline (median EDSS score 5, range 1.5–9.5), no disability progression, clinical relapses or MRI disease activity were reported, and EDSS scores improved (by a median of 2.25 points) in 95% of people at a median follow-up of 30 months (range 12–118 months) after AHSCT[42].

[H2] Progressive MS

On the basis of the evidence reviewed above (see AHSCT in progressive forms of MS), AHSCT is only indicated for people with secondary progressive or primary progressive MS with early and inflammatory-active disease (Figure 1, Box 1). No RCTs have been published, are ongoing or, to our knowledge, are even planned to specifically evaluate AHSCT as a treatment for progressive MS, though BEAT-MS does not exclude participants with secondary progressive MS who meet study entry criteria for disease activity[106].

[H2] Recommendations

- Consider AHSCT as an appropriate escalation therapy for people with highly active MS and for whom high-efficacy DMT has failed (Figure 1, Box 1); this indication should be adopted widely and with equitable access in all geographical areas.
- Refer patients with highly active, treatment-refractory MS as early as possible for consideration of AHSCT.
- In patients with markers of disease aggressiveness: frequent relapses, incomplete recovery from relapses, high frequency of new MRI lesions, rapid onset of disability AHSCT can be considered within a specialized multidisciplinary assessment pathway after failure of a single high-efficacy DMT after a meaningful period of treatment.
- Development and adoption of risk scores and biomarkers to assist clinicians with prompt and robust selection of people who are eligible for AHSCT are encouraged.

- AHSCT as first-line therapy should only be considered for individuals with rapidly evolving, severe MS with a poor prognosis; in this scenario, AHSCT should be offered as part of a clinical trial or an observational, longitudinal research study (if a trial is not available) without delay whenever possible.
- AHSCT can be considered for young (<45 years) individuals with early progressive MS with a short disease duration and who have well-documented clinical and radiological evidence of inflammatory disease.
- Offering AHSCT for progressive MS without detectable inflammatory lesion activity is not supported owing to a lack of evidence.
- Trials to compare AHSCT with approved DMTs for which people with progressive forms of MS are eligible (as per DMT license or marketing authorisation) are encouraged.
- Owing to a high risk and low or no benefit, AHSCT is not recommended for treatment of long-standing, advanced forms of MS with severe disability.

[H1] HSCT in NMOSD

AHSCT and allogeneic HSCT are endorsed by the EBMT as a clinical option and developmental indication for the treatment of NMOSD that is refractory to conventional treatment[2,30]. The indication has reduced in recent years, however, owing to the availability of highly effective pharmacological treatments, including B cell depleting, anti-IL-6 receptor and complement-inhibiting monoclonal antibodies, which effectively suppressed disease activity in RCTs[108].

The role of HSCT in NMOSD has been explored in only a few studies, and outcomes have been mixed[109]. In a registry analysis by the EBMT ADWP that included 16 people with NMOSD who underwent AHSCT with different protocols (BEAM–ATG in 9, thiotepa-Cy in 3 or Cy 200 mg/kg plus ATG in 4), progression-free survival at years 3–5 was 48%, but 81% experienced a relapse at a median of 7 months after AHSCT[110]. Transplant-related mortality was zero. At long-term follow-up (median 47 months), one person had died of disease progression and four had undergone HSCT a second time; three had undergone allogenic HSCT. In 8 evaluable individuals, aquaporin 4 (AQP4) antibodies remained positive at follow-up but these antibodies became undetectable in the 2 evaluable patients of the 3 who subsequently underwent allogeneic HSCT and their absence was associated with durable disease remission.

A prospective open-label cohort study in which 13 people with NMOSD were treated with a complex cyclophosphamine-based protocol (including plasmapheresis the day before hospital admission and two doses of rituximab) produced more impressive results, with progression-free survival of 90% at year 5[111]. Median EDSS scores improved from 4.4 to 3.3, and 80% of individuals were free from relapses and immunosuppressive treatment after 5 years. AQP4 antibodies became negative in 9 of 11 individuals tested, and clearance of autoantibodies was associated with durable disease remission, suggesting that elimination of AQP4 antibodies could be a biomarker of treatment response. No grade IV adverse events or transplant-related mortality occurred.

In a retrospective study of allogeneic HSCT, long-term disease control was reported in a large proportion of individuals with refractory autoimmune diseases, including five individuals with NMOSD, suggesting that this treatment has an acceptable toxicity profile and transplant-related mortality[112]. Durable disease remission for up to 10 years with no detectable AQP4 antibodies was reported in in two individuals who were treated with allogeneic HSCT even after failure of AHSCT[113]. Allogeneic HSCT has also been explored in paediatric NMOSD, with 4 cases logged in the EBMT database of which only in one case outcomes have been reported showing disease control and improvement at 2 years of follow-up[8].

[H2] Recommendations

- Evidence is insufficient to indicate use of HSCT in NMOSD outside of clinical trials, mostly owing to the availability of highly effective treatments.
- AHSCT could be considered as a rescue therapy for NMOSD that does not respond to treatment, or as an induction therapy for aggressive disease, especially with the use of conditioning regimens that include anti-CD20 or antibody-depleting strategies.
- Allogeneic HSCT should only be considered for individuals in whom AHSCT has failed and no other treatment options are available.

[H1] Development of AHSCT services

Neurology and haematology specialists should be involved in the selection of candidates for AHSCT, and an effective AHSCT service requires multidisciplinary expertise and coordination across the areas of neurology, haematology, neuroradiology, physiotherapy, laboratory medicine and reproductive medicine (Table 2). A neurology unit that aspires to

offer AHSCT should have good expertise in the management of MS and/or NMOSD, and experience of AHSCT should be developed through participation in clinical trials or service provision programmes led by neurologists with experience in AHSCT and haematologists with experience in MS in units that comply with the standards set by the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee ISCT–Europe and EBMT (JACIE)[114]. Given the high costs of DMTs, particularly monoclonal antibodies, the time-limited, one-off cost of AHSCT is likely to be a more cost-effective use of resources for the treatment of highly active forms of relapsing–remitting MS, as reported in three studies completed in the USA[115], UK[116] and Norwegian[117] healthcare systems. Appropriate, up-to-date evaluations are needed to inform healthcare payers about AHSCT access and commissioning or repayment policies.

[H2] Recommendations

- Multi-disciplinary expertise and facilities are required for development of an AHSCT service (Table 2).
- Build experience of AHSCT locally through participation in clinical trials or service provision programmes led by neurologists with experience of AHSCT and haematologists with experience of MS.
- For HSCT units, FACT–JACIE or equivalent accreditation is recommended.
- Develop high-quality multidisciplinary regional and national programmes.
- Promote economic evaluations of AHSCT versus licensed therapeutics and appropriate updates in access and funding by healthcare payers.

[H1] Haematological and other specialist assessments

[H2] Assessment of fitness to undergo AHSCT

Assessment of the indication to treat with AHSCT requires detailed neurological assessment with disease history, disability status and MRI examination. Once the indication is established, haematological pre-transplant assessment is required to confirm eligibility and screen for comorbidities that contraindicate the procedure. Standard screening for comorbidities includes liver, bone and viral profiles, measurement of glomerular filtration rate, a lung function test and chest X-ray, cardiac assessment with electrocardiogram and echocardiogram, a dental check-up, identification of fertility needs and assessment of

performance status; an HSCT comorbidity index can be used (Box 1). For individuals whose standard lung function tests are out of range, additional respiratory workup, including chest CT and referral to a respiratory consultant for further assessment, is needed to rule out ventilatory defects. Additional cardiological workup should be done for individuals with considerable cardiac risk factors or those aged >40 years; if any results are abnormal, they should be referred for cardiological review before proceeding to AHSCT. Likewise, any psychological or psychiatric concerns should be evaluated by the appropriate mental health specialist.

The impact of previous DMTs on safety should also be considered, as carryover effects can complicate mobilization, conditioning and immune reconstitution, particularly after treatment with long-acting lymphodepleting agents, such as alemtuzumab, after any cytotoxic treatment, or after multiple lines of therapy. A washout period that is appropriate for previous treatment and host factors is warranted to balance the risks of an MS relapse during DMT withdrawal against that of complications from the sequence of treatments. DMT withdrawal should generally be kept as short as possible to avoid MS disease activity. Specific recommendations for washout periods before leukoapheresis and lymphodepleting conditioning treatment have been published by the EBMT[118]; however, given that clinical and medication histories are often complex for individuals considering AHSCT, we recommend discussion and decision-making among a multidisciplinary expert group on an individual case basis.

[H2] Management of fertility

MS is prevalent in young adults and especially women of childbearing age. Furthermore, demographic shifts mean that the age of women at childbirth is increasing in developed countries, suggesting that an increasing proportion of individuals with MS who are referred for AHSCT will still hope to become pregnant after the procedure. Successful pregnancies after AHSCT (mostly through natural conception) have been reported in the retrospective EBMT survey of AHSCT in autoimmune diseases without any apparent effects of conditioning regimens or increased risk of disease reactivation after delivery, though the numbers were small and the data were not corrected for the desire for pregnancy[119]. In retrospective studies of people who have undergone AHSCT for MS, the rate of menses recovery was 52% after use of the BEAM–ATG protocol[38] and 70% after use of the cyclophosphamide–ATG protocol[120]. **[Au: Edited wording OK?OK]** In the latter study,

older age and prior use of cyclophosphamide were associated with persistent amenorrhoea after AHSCT[120]. Evidence from large, well-designed prospective studies is lacking.

Importantly, however, spontaneous resumption of menses might not be an accurate marker of fertility in this context, as anti-Mullerian hormone **[G]** (AMH) was low even in individuals in whom menses resumed[120], and natural conception has been reported despite post-transplant amenorrhoea[121] and low AMH levels[122]. Hence, contraception is not only mandatory before starting cytotoxic chemotherapy or any other agent that is teratogenic or contraindicated in pregnancy, but also recommended in the early post-transplant period, and thereafter if a pregnancy is not desired, even in women with amenorrhoea. Hormonal replacement therapy should be considered in women diagnosed with premature ovarian failure[123]. In addition, autoimmune diseases that warrant AHSCT might be associated with reduced fertility at baseline[124,125] (which may be undiagnosed), possibly increasing the risk of permanent amenorrhoea after the procedure[124]. Evidence indicates that gonadotropin-releasing hormone (GnRH) agonist treatment before AHSCT is effective in protecting the ovaries from chemotherapy-related premature ovarian failure and maintaining ovulation[123,126], yet evidence for benefit on fertility preservation was considered insufficient and requires further investigation[126].

Impairment of fertility is reported in males who underwent HSCT for haemato-oncological indication at rates between 20%-90% depending on the conditioning regimen[127] but few data are available in the autoimmune setting, showing a reduction in testosterone level compared to the pre-treatment (although remaining above the defined threshold in three out of four tested patients)[124]. In male MS patients, disorders of the reproductive organs and fertility after AHSCT with BEAM-ATG or cyclophosphamide-ATG protocols were reported at an incidence rate of roughly 28/1,000 person-years[128]. Sporadic cases of unassisted fertilization resulting in conception after AHSCT in MS have been reported [53,121].

[H2] Recommendations

- Perform an accurate haematological assessment before AHSCT to confirm eligibility and to screen for comorbidities (Box 1).
- Manage the risks of toxicity and carryover effects from prior treatments with an appropriate washout period; this period should not be longer than necessary because withdrawal of DMTs increases the risk of MS activity and neurological deterioration.

- Assess, counsel and refer individuals for provision of personalised information and management of their reproductive needs, fertility risk and contraception before initiation of treatment.
- Emphasize to patients that use of contraception in the pre-transplant to early post-transplant period is essential, even for those who are expected to have reduced fertility.
- Facilitate access to reproductive endocrinology or gynaecology services before AHSCT for counselling and preservation of fertility for both male and female candidates, and after AHSCT for treatment of premature menopause in females and of sub-fertility and hypogonadism in males.
- Reproductive specialists are encouraged to include in the endocrine workup before AHSCT the measurement of follicle-stimulating hormone, luteinizing hormone, oestradiol, anti-Mullerian hormone (in females) and testosterone (in males).
- When appropriate for the patient, specialists should consider treatment GnRH agonist to attenuate the risk of premature menopause.

[H1] AHSCT treatment methodology

[H2] Treatment protocols in MS

Given that lympho-ablative conditioning has a key role in the mechanism of AHSCT, a correlation between the intensity of the regimen and neurological outcomes has been postulated[62,63,129]. Though low-intensity regimens (for example, lower-dose cyclophosphamide without serotherapy) were ineffective in one study[130], evidence for the proposed correlation is lacking. Intensive conditioning protocols (for example, cylophosphamide–total body irradiation–ATG or busulfan–cyclophosphamide–ATG are likely to be more effective but also to be associated with a higher risk of toxicity[129]. For these reasons, intermediate-intensity conditioning protocols, such as BEAM–ATG or cyclophosphamide–ATG, have been widely adopted for AHSCT treatment of MS; use of the latter has increased over the past ten years owing to the relatively easier inpatient management and the influence of the MIST trial[81] amongst other factors. The current EBMT guidelines advocate use of either the cyclophosphamide–ATG or BEAM–ATG regimens delivered in transplant units that provide high-quality care and are accredited by JACIE or equivalent organizations[30].

The efficacy and safety of BEAM–ATG and cyclophosphamide–ATG regimens have been compared only in retrospective studies. In one such comparison in relapsing–remitting MS, use of the BEAM–ATG conditioning protocol was independently associated with a higher chance of NEDA-3 maintenance than other intermediate-intensity or low-intensity regimens, though the number of individuals who were treated with the standard cyclophosphamide–ATG conditioning protocol was very low (27 people)[44]. More evidence is expected from a retrospective analysis of the EBMT database to compare efficacy and safety outcomes in a larger cohort (n = 1,114) of people with MS who were treated with either BEAM–ATG (n = 442) or cyclophosphamide–ATG (n = 672) regimens between 1998 and 2018. From a preliminary report of this analysis[131], no statistically significant differences were detected in either the effectiveness or the toxicities of the two regimens when adjusted for disease type (progressive versus relapsing–remitting), EDSS score at baseline and year of the procedure.

The ECTRIMS Focused Workshop attendees agreed that a personalized medicine strategy in which the AHSCT protocol is tailored to individuals according to disease activity and risk profile is worth exploring. When assessing the treatment intensity required, [the use of chemotherapy in the mobilization regimen, graft manipulation (i.e. CD34 selection to enrich for HSC or not) and the use and type of serotherapy should also be considered in addition to the conditioning regimen used. Differences in the ability of chemotherapy drugs and immunosuppressive treatments to penetrate the CNS, which may affect their efficacy in suppressing the immune attack in the target organ should also be considered in the choice of conditioning regimen. In making the choice, any previous treatments, particularly cytotoxic drugs should also be considered as cumulative toxicities may increase the risk of AHSCT.

[H2] Treatment protocols in NMOSD

Evidence in NMOSD is limited because only a small number of individuals have been treated with heterogeneous treatment protocols and comparative studies are lacking. A retrospective study by the EBMT showed that the majority of people who underwent AHSCT for NMOSD with various conditioning regimens experienced subsequent relapses and neurological deterioration in the long term[110]. Evidence from a single-centre study suggests that addition of rituximab and/or plasmapheresis to the conditioning regimen improves outcomes after AHSCT for NMOSD — use of a complex protocol that included rituximab led to markedly better outcomes than in previous studies, inducing disease remission and clearance of AQP4

antibodies in 9 of 11 participants over a median 5-year follow-up period[111]. However, further evidence is needed to confirm this finding.

Allogeneic HSCT for NMOSD mainly involves use of HSCs from HLA-matched donors, and myeloablative conditioning regimens that include serotherapy with ATG or alemtuzumab. Safety has improved over time, yet complications and transplant-related mortality remain higher than with AHSCT[132,133]. In the EBMT registry study, factors associated with improved PFS were age <18 years, male sex and undergoing the procedure more recently[112]. Accordingly, allogeneic HSCT could be a treatment option only when conventional treatment has failed and relapses continue after AHSCT, but further studies are needed to determine the optimal approach. In this context, future strategies to reduce the risks include exploring new conditioning regimens with lower toxicity and/or different approaches to graft-versus-host disease prophylaxis, such as post-HSCT cyclophosphamide.

[H2] Recommendations

- For the treatment of MS, intermediate-intensity conditioning protocols, such as BEAM–ATG or cyclophosphamide–ATG, are recommended to achieve the best balance of efficacy and risk in most settings, according to EBMT guidelines.
- The use of low-intensity regimens (for example, low-dose cyclophosphamide without serotherapy) is not recommended outside clinical trials owing to poor evidence of efficacy.
- Use of high-intensity, myeloablative conditioning protocols (for example busulfan–cyclophosphamide–ATG) is not recommended outside clinical trials owing to a higher risk of toxicity, but can be considered at a centre with the specific expertise.
- For the treatment of NMOSD, when indicated, cyclophosphamide-based conditioning protocols, possibly associated with rituximab, are appropriate; the role of allogeneic HSCT is confined to a rescue treatment option for when NMOSD does not respond to approved biological therapy and relapses continue after AHSCT.
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[H1] Neurological care after AHSCT

[H2] Rehabilitation

Rehabilitation for individuals with MS in whom AHSCT completely suppresses inflammation is a unique opportunity to exploit the reorganizational capacity of the brain and

achieve maximal clinical recovery. Recommendations for rehabilitation in people with MS who undergo AHSCT[134] include four phases (Table 3). ECTRIMS Focused Workshop attendees agreed on the need for further research in this field to clarify issues such as the optimal timing and setting of treatment, the type and intensity of exercises during the acute phase, and the potential additive effects of rehabilitation on neurological outcomes.

[H2] Clinical monitoring

In MS, disability outcomes are mostly based on changes in EDSS scores, but the low sensitivity of this scale to changes, especially for baseline scores close to six, make it suboptimal for assessment of treatment effects[135]. Combination of the EDSS with other disability measures, such as the Multiple Sclerosis Functional Composite (MSFC)[136], is therefore warranted; this combination has already been implemented in some studies of AHSCT[63,81]. Use of more sensitive tools should also be explored; for example, longitudinal changes in accelerometry data[137] could be useful for assessing disability worsening beyond an EDSS score of 4.0. In order to better define the main driver of disability accrual after AHSCT, we suggest separation of confirmed disability accrual into relapse-associated worsening and PIRA[138]. In people with relapsing–remitting MS, prevention of conversion to secondary progressive MS would be a highly relevant endpoint but can only be evaluated in long-term studies. Cognitive outcomes should also be systematically assessed with the most appropriate instruments in the clinical setting, as such assessments could provide the most sensitive measure of overall brain function. Validated and standardized patient-reported outcomes, including fatigue and QoL measures, should be collected in prospective studies, and use of new technologies, such as smartphones, wearable devices and sensors for data collection should be explored[89].

[H2] MRI monitoring

The MRI metrics that have been most commonly reported in studies of AHSCT are the numbers of new T2 and gadolinium-enhancing lesions. Across multiple studies, suppression of MRI inflammatory activity for at least 3–5 years was observed in most people who were treated with AHSCT[71,139], with complete suppression of gadolinium-enhancing lesions for up to 12.7 years after high-intensity regimen AHSCT in one study[129]. Reductions in T2 lesion load have also been reported[14,62]. In both published RCTs in which AHSCT was compared with DMTs, MRI outcomes were superior with AHSCT[80,81].

Brain volume changes have been explored in fewer studies, but these studies have indicated that brain volume loss slows in the mid-to-long term after AHSCT to rates that are comparable with those in healthy individuals[63,129]. This slowing usually follows a transient increase in the rate of loss in the first 1–2 years after AHSCT, which could result from a combination of pseudo-atrophy and neurotoxic effects related to the intensity of the conditioning regimen[77].

The ECTRIMS Focused Workshop attendees agreed that evaluation of MRI outcomes after AHSCT requires dedicated protocols, and that the Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) guidelines[90] could be applied for standardization in this setting. A so-called re-baseline MRI should be acquired 6 months after AHSCT to serve as a new reference for assessment of post-therapy MRI lesion-based outcomes, while a later re-baseline MRI is required for assessment of brain atrophy to account for the pseudo-atrophy effects described above. Advanced MRI measures, including structural and functional connectivity, remyelination metrics and emerging biomarkers such as paramagnetic rim lesions, could provide new insights into the effects of AHSCT in MS in future studies.

[H2] Management of MS reactivation and DMTs

Information that is useful for the management of MS reactivation after AHSCT is sparse because the rate of events has been low. Even when MS reactivations have been reported[140], few details have been provided about the criteria used for reintroduction of DMTs, neurological outcomes after follow-up and the safety of further treatment with DMTs. For these reasons, evidence-based recommendations for this scenario cannot be provided.

Attendees of the ECTRIMS Focused Workshop were in consensus that MS reactivations that occur between mobilization and conditioning, occurrence of which is usually related to the time between these steps and previous treatment received, do not require resumpion of DMTs. Reactivations that occur after completion of the AHSCT protocol should be managed on an individual case basis. In studies of AHSCT with follow-up periods >5 years, DMTs were reintroduced in 11–35% of individuals[51,141]. In one study examining long-term clinical outcomes after AHSCT, retreatment with DMTs was reported in 15% of patients and the retreatment started after 2 median years (range 0.5–13 years). In the re-treated subgroup, moderate-efficacy DMT were prescribed in 60% of cases and high-efficacy DMTs in 40% [44]. [of DMTs followed MS relapses in most cases, but also sole detection of MRI activity in some[14,139]. DMTs were usually not reintroduced in the case of PIRA, as their benefits in this context are currently unknown.

When reintroducing a DMT after AHSCT, the safety of the treatment should be considered particularly carefully. Though one study showed that the risk of infections at 12 months was comparable in people who had undergone AHSCT and people who received non-induction DMTs[128], the risk of adverse events might be increased by previous exposure to high-dose immunosuppression due to cumulative effects lowering immune competence. Furthermore, MS inflammatory activity can occur after reintroduction of DMTs, mostly when using first-line DMTs and when reintroduction was due to an MS relapse rather than MRI activity. The role of a second AHSCT, including for those who have had a prolonged response to a first AHSCT, is currently under evaluation by the EBMT ADWP. Given that evidence is lacking, neurological and safety outcomes after MS reactivation require further investigation, preferably in large collaborative studies.

[H2] Recommendations

- Facilitate access to rehabilitation services that cover the four recommended phases (Table 3).
- After AHSCT, monitor neurological outcomes, including relapses and disability metrics; to assess disability, use the EDSS, MSFC and other established rating scales, as well as more advanced instruments where available. [
- Consider collecting measures of cognitive function, fatigue and QoL.
- Explore new technologies such as wearable electronic devices and biosensors for collecting patient-reported outcomes.
- Monitor MRI outcomes according to MAGNIMS guidelines; acquire images before HSC mobilization, a re-baseline scan 6 months after AHSCT, and yearly scans thereafter, or as clinically required.
- Consider reintroducing DMT if a relapse occurs after AHSCT on an individual case basis, paying special attention to additional risks from all previous treatment exposures.

[H1] Prophylaxis and care of complications

[H2] Risk of infection and vaccinations

In addition to the extent of experience at the centre, several factors can influence the risk of infection for people who have undergone AHSCT, including epidemiological factors (for

example, influenza season or the presence of small children in the household), previous disease such as recurrent urinary or respiratory infections, prior immunosuppressive treatment received, prior immunization history, transplantation-related factors (for example, the type of chemotherapy used, use of irradiation, HSC purification or T cell depletion of the haematopoietic graft, and the use of B-cell depleting antibodies either as DMT before AHSCT or after AHSCT for treatment of post-transplantation reactivation of Epstein–Barr virus (EBV).

Published guidance recommends that people who have undergone HSCT are considered as 'never vaccinated' and offered revaccination[142]. Vaccination planning after AHSCT should follow national[142] and international recommendations[143] and be adapted to local practice. Vaccination can follow a routine schedule or flexible timepoints based on immunity milestones; the latter maximizes the likelihood of response but also carries a higher risk of missing vaccinations. No evidence suggests a major risk of direct adverse effects from inactivated vaccines in immunocompromised individuals, and existing data indicate only very low risks of complications associated with immune activation, such as rejections or disease exacerbation[143]. By contrast, vaccine-induced infectious disease has been associated with administration of live vaccines, especially in people with suppressed T cell immunity, and outcomes can be severe[143]. The ECTRIMS Focused Workshop attendees recommended harmonization of vaccination protocols within regional or national AHSCT programmes, regular (e.g. annual) review and updates of protocols as necessary to ensure coverage of emerging indications as required for disease outbreaks from new pathogens or variants (for example, COVID-19).

The main infections to be considered in people who have undergone AHSCT for MS include pneumococcal disease, influenza virus infection, varicella zoster virus (VZV)-related infections, and COVID-19. In a meta-analysis of invasive pneumococcal disease in immunocompromised individuals, the risk of severe invasive pneumococcal disease was increased in recipients of AHSCT compared with that in healthy controls, though the data were not stratified according to the underlying disease[144]. The 2017 European Conference on Infections in Leukaemia (ECIL7) guidelines[143] suggest that recipients of AHSCT should receive three doses of conjugated anti-pneumococcal polysaccharide vaccine administered at 1-month intervals starting from 3–6 months after transplantation, followed by one dose at 12 months. One dose of annual seasonal inactivated influenza vaccination is recommended at the beginning of the flu season in all recipients of AHSCT at 3–6 months after transplantation, particularly for those who are considered to be immunosuppressed[143]. In case

of an influenza outbreak in the community, vaccination could be administered before 6 months, but should not be administered less than 3 months after transplantation in any case[142]. In a clinical trial, two doses of the recombinant VZV vaccine effectively prevented herpes zoster in people who had undergone AHSCT[145]. Given the high risk of herpes zoster in the first 2-3 years after HSCT, recent guidance recommends vaccination with the recombinant VZV vaccine commencing 6 months after transplant and the article provides the schedules, cautions and contraindications for this as well as other vaccinations [142]. With respect to SARS-CoV-2 vaccination, the effects of DMTs on antibody-mediated responses in MS have been extensively studied[146], but few data are available in people who have undergone AHSCT for MS, so a standard schedule should be adopted according to national and international guidelines[147].

[H2] Viral reactivations

Comprehensive data on viral infection and reactivation after AHSCT for autoimmune diseases, including MS, are lacking. CMV reactivation has been reported in 11–35% of people who have undergone AHSCT for MS[45,148,149], and EBV reactivation after AHSCT for treatment of MS has been reported in 34–100%[51,148–150]. The discrepancies between studies could be attributed to differences in treatment protocols, the methodology used for testing, the frequency of testing, the definitions of reactivation used and/or differences in the patient populations, which could also be influenced by previous treatment. The risk of EBV reactivation is increased by addition of T cell-depleting strategies (for example, alemtuzumab or ATG, especially at higher doses)[151], use of a high-intensity conditioning regimen and the MS disease itself, since the high prevalence of EBV in people with MS[152], yet the occurrence of EBV disease or EBV-associated post-transplant lymphoproliferative disorder (EBV–PTLD) is rare and can be managed with current monitoring and pre-emptive strategies[153]. Use of B cell depleting CD20 antibody therapy in the period before AHSCT could protect against EBV reactivation in theory by eliminating EBV-infected B cells, the main reservoir of the virus, but, to our knowledge, this hypothesis is yet to be tested. More research is needed on reactivation of CMV and EBV, their management and outcomes after AHSCT; an ADWP survey on this topic is underway.

Nevertheless, current EBMT guidelines recommend screening for cytomegalovirus (CMV), herpes simplex virus (HSV), VZV, EBV, HIV, human T-lymphotropic virus type 1 and 2, and hepatitis viruses as part of the pre-transplantation workup[154]. Testing positive for HIV, HSV, HTLV-1 and hepatitis viruses does not represent per se a contraindication to

AHSCT but the conditions and any associated disease or treatments should be considered in the evaluation of risk and in the management of the patient candidate to AHSCT. For individuals who are positive for antibodies against CMV and EBV and who receive ATG, other serotherapy or manipulated autografts, the same guidelines recommend monitoring for reactivation of these viruses for the first 100 days[154]. To monitor for CMV and EBV reactivation, standardized PCR assays are recommended, at least during the highest risk period (days 15–60), with weekly testing in the first 2 months, then fortnightly until day 100.[154]

For CMV, pre-emptive treatment of laboratory-detected viral reactivation with valganciclovir or ganciclovir should follow local or national guidelines, and treatment of CMV-related disease, which is exceedingly rare, is always recommended. EBV reactivation associated with monoclonal paraproteinemia has been associated with adverse neurological events and lymphoproliferative disease[155-157]. To mitigate the risks, following EBV reactivation, active surveillance for post-transplant lymphoproliferative disease according to local practice is recommended[154]. Pre-emptive treatment with rituximab should be considered for people who are at high risk of EBV–PTLD and impaired immune reconstitution such as patients with high peak EBV viral load post-AHSCT[155].

Another important virus that must be considered is John Cunningham virus (JCV), as failure to control latent infection of JCV in the brain can cause progressive multifocal leukoencephalopathy (PML), which is a known risk of treatment with natalizumab[158] and, less commonly, other MS DMTs[159–160] that can cause long-lasting CNS injury and in severe cases be fatal. PML has been reported as a rare complication after AHSCT for the treatment of haematological malignancies, but only 11 cases were reported up to 2017[161], and, to our knowledge, no cases of PML have been reported after AHSCT for the treatment of MS.

[H2] Secondary autoimmunity

Autoimmune complications that can occur after AHSCT include organ-specific involvement and systemic diseases, but the incidence, risk factors, treatment and outcomes of these complications are not well characterized. So-called secondary autoimmune diseases have been described in 2–18% of people who have undergone AHSCT for MS[64,162], with some differences between transplantation regimens, but these complications are thought to be under-reported. The main secondary autoimmune diseases that have occurred in people with MS are thyroiditis and, less frequently, idiopathic thrombocytopaenic purpura (ITP), but

other disorders that have been described include Crohn disease, acquired autoimmune factor VIII deficiency and alopecia areata[163].

A review of the available literature published in 2021 determined that a high risk of secondary autoimmune diseases was associated with the use of high-intensity myeloablative conditioning regimens that involve use of busulfan, after which the overall incidence was 18% across multiple studies [57]. By contrast, intermediate-intensity non-myeloablative conditioning regimens were associated with lower incidence (7.7%) overall, though regimens that involved used of alemtuzumab were associated with an incidence of 14% in one study[163], and with a higher risk of idiopathic thrombocytopaenic purpura (incidence 11.5%) when compared with regimens that used ATG in another study[45]. Secondary autoimmunity is a known complication of alemtuzumab treatment in MS, and a comparison of alemtuzumab treatment with AHSCT for MS showed that the risk of thyroid disease was higher with alemtuzumab[54,128], though the incidence of thyroid disease was higher in both groups than in those who received non-induction therapies[128]. These observations suggest that higher vigilance for secondary autoimmunity could be warranted for people who had received alemtuzumab before to AHSCT.

In the same review, pooled rates of secondary autoimmune diseases were <1% after use of BEAM regimens[163], though this low rate could be due to under-reporting. Indeed, in a retrospective study, AHSCT with use of either BEAM–ATG or cyclophosphamide–ATG regimens[128] was associated with an 11% incidence of autoimmune thyroiditis in the first 3 years, almost sixfold the incidence in a reference group treated with any of 4 therapies that comprised rituximab, fingolimod, natalizumab, and dimethyl fumarate, [128]. One possible strategy to decrease the risk of secondary autoimmunity after AHSCT is post-transplantation B cell depletion; this approach has been tested in a small group of people who were receiving alemtuzumab treatment[164], in whom rituximab therapy seemed to prevent secondary autoimmunity, so use of this approach in the context of AHSCT warrants further investigations.

[H2] Late adverse events

Besides secondary autoimmune diseases and effects on fertility, other delayed adverse events of AHSCT mainly include risk of infection and malignancies. Data on the frequency of these events after AHSCT for autoimmune diseases and how strongly they are related to the treatment are sparse, and limited information is available on other potential long-term complications, such as cardiovascular and bone mineral diseases. The risk of infections

(mainly pneumonia and VZV reactivation) is considered highest during the first 2 years after AHSCT, but systematic evidence is lacking. Standard management of such infections includes antibiotic prophylaxis to cover invasive fungal infections for the first 3–4 months after AHSCT and herpes virus and pneumocystis infection for 6 months, alongside immune monitoring for T cell and B cell subsets and immunoglobulin electrophoresis (on a 3-month basis in the first year and then annually) to guide infection prophylaxis[30].

Though concerns exist from data in the oncology field that chemotherapy can be associated with an increased life-time risk of malignancy,[165] no current evidence suggests this to be the case in a non-malignant (that is, autoimmune) primary disease setting. In an ongoing retrospective study of the EBMT–ADWP Registry that includes ~500 individuals who have been treated with AHSCT for various autoimmune diseases (47% MS) at 27 participating centres in 11 countries during the period 1997–2016, predictive cumulative incidence of malignancies, endocrine or bone complications and cardiac complications at year 10 were 3.5%, 20.3% and 13.1%, respectively[166]. A similar risk of malignancies was reported among people with MS in a previous EBMT–CIBMTR Registry study[64]. However, the low numbers of events and possible contributions of previous exposure to immunosuppressive treatments prevents accurate estimation of the risk of malignancy after AHSCT.

[H2] Recommendations

- Offer revaccination after AHSCT according to local, national and international (ECIL7) recommendations
- Monitor for CMV and EBV reactivation with standardized PCR assays, at least over the highest risk period (day 15 – 60), with a weekly schedule in the first 2 months, and then fortnightly until day +100.
- Watch and treat or refer promptly for secondary autoimmune disease; these mainly present as thyroiditis or idiopathic thrombocytopenic purpura, but be aware of less common diseases such as autoimmune haemolytic anaemia, acquired haemophilia, antiphospholipid syndrome and myasthenia gravis.
- Collect long-term survival data and use standardized surveillance tools to capture and report late adverse events, with particular attention to late infections and malignancies.

[H1] Conclusions

Immunological studies provide increasing support to the hypothesis that 'immune resetting' is the mechanism of action of AHSCT in MS. Refinement of treatment protocols and patient selection has improved the efficacy and safety of the procedure. Uncontrolled cohort studies and meta-analyses have shown that among people with relapsing–remitting MS for whom standard treatment has failed, AHSCT has high effectiveness with acceptable safety, and two RCTS have shown that its efficacy is greater than of moderate-efficacy and some high-efficacy DMTs (mitoxantrone and natalizumab).

In this Consensus statement, ECTRIMS and the EBMT, as well as lead representatives of ACTRIMS, endorse AHSCT for selected indications. In relapsing–remitting MS, AHSCT should be offered to appropriate candidates, normally after failure of high-efficacy DMT but within the window of opportunity before the development of irreversible disability. More evidence to inform the optimal positioning of AHSCT in MS care is awaited from ongoing RCTs in which AHSCT is being compared with high-efficacy DMTs in relapsing–remitting MS. AHSCT is not recommended in any late-stage forms of MS that are typically progressive, although could have a role in early progressive disease with clear clinical and/or radiological evidence of inflammation. AHSCT with adapted protocols can be considered for treatment-refractory NMOSD.

Improved outcome measures that sensitively and accurately capture all domains that are relevant to patients are needed in future studies of AHSCT. We recommend that long-term objective neurological assessments, MRI data and patient-reported outcomes are systematically collected from all individuals who undergo AHSCT at all centres worldwide, including those that offer low-intensity protocols in an outpatient setting, so that adequate evidence can be assessed and included in meta-analyses. To advance knowledge on the biological effects and mechanisms of action of AHSCT, further studies of immune reconstitution and immune function are needed, making use of inflammatory, neuro-axonal and glial biomarkers. Advances in knowledge will be maximized through collaborative research in registry-based studies, large cohort studies and multi-centre trials.

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Table 1 | Features of ongoing randomized clinical trials of haematopoietic stem cell therapy in multiple sclerosis.

Feature of trial	RAM-MS	BEAT-MS	STAR-MS	NET-MS
Registry identifier	NCT03477500	NCT04047628	EudraCT N 2019-001549-42	EudraCT N 2022-002654-95
Countries	Norway, Denmark, Sweden, Netherlands	USA	UK	Italy
Criteria for eligibility				
MS subtype	RR-MS	R-MS	RR-MS	RR-MS
Age range (years)	18–50	18–55	16–55	18–55
MS duration (years)	Not reported	Not reported	≤10	Not reported
EDSS score	0.0–5.5	0.0–6.0	0.0–6.0[a]	2.0–6.0
Prior DMT failure required	Standard DMT (IFNβ, glatiramer acetate, dimethyl fumarate, teriflunomide, fingolimod, natalizumab)	Oral DMT, monoclonal antibody approved by the FDA for R-MS, or rituximab	Standard DMT (not required for people with rapidly evolving severe MS)	Oral DMT or monoclonal antibody (≥6 months treatment)
Disease activity required	≥1 clinical relapse and MRI activity in the previous year (relapses must have occurred ≥3 months after initiation of DMT)	≥2 episodes of disease activity (relapse or MRI) in the previous 36 months[b]	≥1 clinical relapse or MRI activity in the previous 12 months despite DMT	≥1 relapse and MRI activity in the previous 12 months
Definition of MRI activity	≥1 Gd or ≥3 new or enlarging T2 lesions	≥1 unique active lesion (either 1 Gd or 1 new T2 lesion)	≥2 new or enlarging T2 lesions	≥1 Gd or ≥1 new T2 lesion
Treatment and outcomes				
AHSCT Conditioning	Cy + ATG	BEAM + ATG	Cy + ATG	BEAM + ATG
Comparator	Alemtuzumab, cladribine, ocrelizumab	Alemtuzumab, cladribine, natalizumab, ocrelizumab, ofatumumab, rituximab, ublituximab	Alemtuzumab, cladribine, ocrelizumab, ofatumumab	Alemtuzumab, natalizumab, ocrelizumab, ofatumumab
Primary endpoint	NEDA-3	Relapse-free survival	NEDA-3	NEDA-3

[a]If the EDSS score is 0–1.5, the following criteria must also be fulfilled: short illness duration (<5 years), clinically and radiologically active disease (that is, at least two relapses in the past 12 months and evidence of multiple gadolinium-enhancing MRI lesions), a high brain lesion load, and brain or spinal cord atrophy. An EDSS score of 6.0 must be due to confirmed relapse rather than progressive disease. [b]≥1 episode must be a relapse, ≥1 episode must have occurred within 12 months before screening, and ≥1 episode must occur after ≥1 month of treatment with DMT. ATG, anti-thymocyte globulin; Cy, cyclophosphamide; BEAM, busulfan, etoposide, carmustine and melphalan; DMT, disease-modifying therapy; Gd, gadolinium-enhancing; NEDA-3, no evidence of disease activity; PML, progressive multifocal leukoencephalopathy; R-MS, relapsing multiple sclerosis; RFS, relapse-free survival; RR-MS, relapsing–remitting multiple sclerosis.

Table 2 | Main components of a haematopoietic stem cell transplantation service

Unit	Setting	Contribution to HSCT service
Neurology	Outpatient	– Screening for HSCT eligibility – Pre-HSCT assessment of neurological status – Post-HSCT monitoring (focused on effectiveness outcomes)
Haematology	Outpatient and inpatient	– Screening for HSCT eligibility (exclusion of contraindications) – Mobilization and collection of HSCs – Conditioning, HSC reinfusion and recovery – Post-HSCT monitoring (focused on safety outcomes, including late effects)
Neuroradiology	Outpatient	– Screening for eligibility – Post-HSCT monitoring (focused on MRI outcomes)
Physiotherapy	Outpatient and inpatient	– Pre-habilitation – Post-HSCT rehabilitation
Laboratory	Outpatient and inpatient	– Screening investigations in blood, CSF, bone marrow and other biological samples – Safety monitoring with blood biochemistries and diagnosis and monitoring of infections – Investigation of immune recovery
Reproductive Medicine	Outpatient	– Fertility counselling before and after HSCT – Fertility preservation – Assisted reproductive technology
Health Psychology and Neuropsychology	Outpatient	– Psychological assessment before HSCT – Psychological counselling before and after HSCT – Neuropsychological testing before and after HSCT – Psychiatric evaluation if screening raises concerns

HSC, haematopoietic stem cell; HSCT, HSC transplantation.

Table 3 | The phases of rehabilitation for people who undergo autologous haematopoietic stem cell transplantation.

Phase	Timing[a]	Setting	Assessment and treatment activities
1	Weeks –4–0	Outpatient	Assessment and 'pre-habilitation'. Baseline level of functional impairment should be ascertained, including the identification of risk factors for deterioration, with the aim of optimizing physical, social and emotional functioning and wellbeing before AHSCT. The scope of 'pre-habilitation' is to enhance neuromuscular systems and respiratory function, and to reduce the risk of secondary complications. It includes breathing and cardiovascular exercises, management of spasticity, fatigue and pain, and cognitive rehabilitation.
2	Weeks 0–4	Inpatient and early after discharge	Acute rehabilitation is patient-centred and helps to prevent hospitalization-related complications through gentle mobilization and optimization of respiratory function. Intensity of exercises should be adapted to platelet counts; exercise is contraindicated if platelet counts are below 20 $x10^9$/l. Strict infection control measures should be in place. Individual symptoms (for example, spasticity) should be assessed and treated promptly.
3	Usually weeks 8–12	Outpatient	Subacute rehabilitation is a period of intense inpatient or outpatient rehabilitation that starts when the individual is medically stable. The aim is to optimize physical fitness, independence and the outcome of transplantation, and to treat neurological problems and any the other disabilities.
4	Weeks 12–26	Outpatient	Community rehabilitation, including vocational rehabilitation, after discharge from the hospital – this recovery phase is a continuation of the inpatient goals within the home environment. Aim is to integrate the individual back into their home life, promote independence and possibly help to recover working activities.

[a]Time in relation to the day of haematopoietic stem cell reinfusion. AHSCT, autologous haematopoietic stem cell transplantation.

Box 1 | Recommendations for selection of people with multiple sclerosis haematopoietic stem cell transplantation

Neurological assessment

General suitability profile

- Age <45 years
- Disease duration <10 years
- Rapidly evolving severe and/or treatment-refractory inflammatory active MS
- EDSS <6.0[a]
- Capacity to give informed consent and to adhere to HSCT schedule
- Markers of disease aggressiveness: frequent relapses, incomplete recovery from relapses, high frequency of new MRI lesions, rapid accumulation of disability

Additional profile for suitability in relapsing-remitting MS

- After failure of any one high-efficacy DMT
- Regardless of previous DMT failure: rapidly evolving severe MS with poor prognostic factors (highly restricted indication, should be offered only in a clinical trial or study)

Additional profile for suitability in progressive MS (primary or secondary)

- Early, active disease forms
- Recent (<12 months) evidence of inflammatory activity (confirmed relapse and MRI)
- Clinical progression with rapid worsening of disability despite treatment with DMT
- Favourable risk profile (young age, no relevant comorbidities)

Haematological assessment required

- Renal and bladder function, liver and bone profiles
- Screening for infective diseases
- Lung function test and chest X-ray (additional respiratory work-up may, including CT-chest and respiratory review, as needed)
- Cardiac assessment with electrocardiogram and echocardiogram (additional cardiological work-up may and cardiological referral, as needed)
- Dental check-up
- Fertility discussion and referral if appropriate
- Performance status
- Psychological and mental health evaluation

Major contraindications for AHSCT in MS

- Active neoplasia or concomitant myelodysplasia
- Acute or chronic uncontrolled infection
- Uncontrolled psychiatric disease or any other condition that raises the risk of poor adherence to treatment regiment

[a] Some patients with EDSS >6.0 may be suitable for AHSCT if the increase above EDSS 6.0 was caused by MS relapse in the previous few months suggesting acute inflammatory activity rather than chronic neurodegenerative processes. AHSCT, autologous HSCT; DMT, disease-modifying therapy; EDSS, expanded disability status scale; HSCT, haematopoietic stem cell transplantation; MS, multiple sclerosis.

Figure 1 | Suitability for autologous haematopoietic stem cell transplantation as a treatment for multiple sclerosis. Neurological (top) and haematological (bottom) variables on the left are associated with a positive recommendation (green profile) for autologous haematopoietic stem cell transplantation (AHSCT). The numbers (age, disease duration, EDSS score) are indicative to illustrate the principles but are not intended as cutoff values. The profile on the far left therefore represents the ideal candidate for AHSCT. Variables on the right are adverse factors and, when they are prevalent, AHSCT is not recommended (red profile). Specific considerations for relapsing–remitting multiple sclerosis (MS) and progressive MS are shown in the central boxes with traffic light indicators of suitability for AHSCT. DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; HE-DMT, high-efficacy DMT; ME-DMT, medium-efficacy DMT. [a]AHSCT could be considered in older, biologically fit people on an individual basis. [b]Within a clinical trial or study.

Glossary

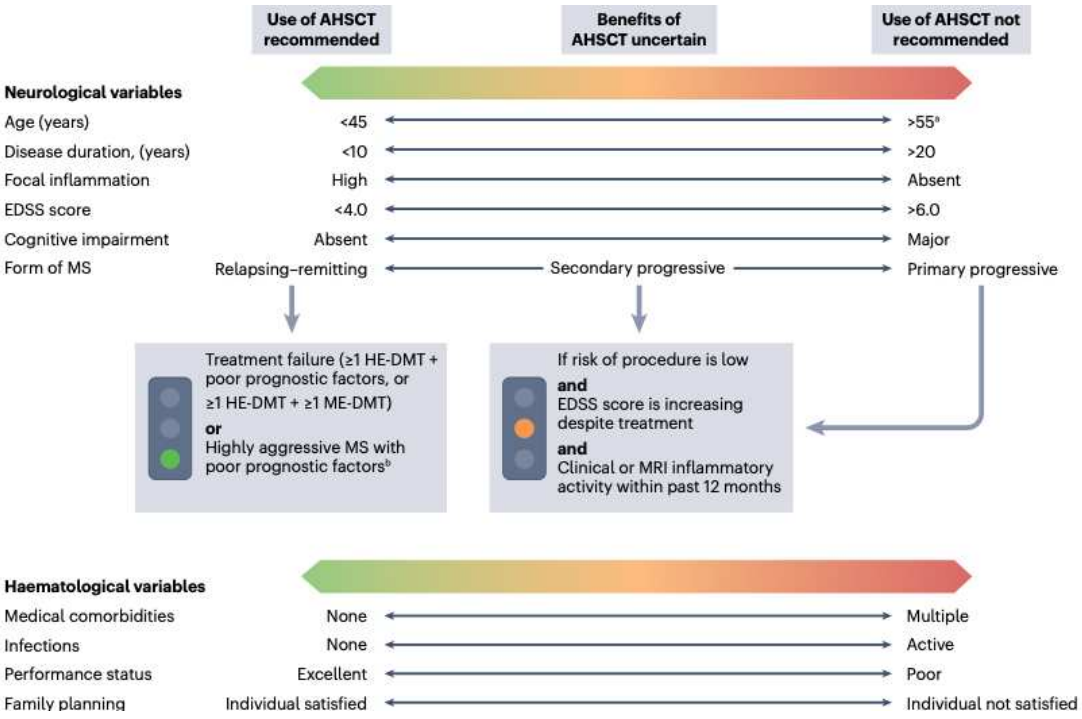
Switched memory B cells: long-lived B cells that have undergone class switch recombination, enabling them to produce antibodies of different isotypes (such as IgG or IgA) while retaining memory of a specific antigen.

Progression-free survival: survival in the absence of neurological deterioration as measured by the Expanded Disability Status Scale (EDSS) score assessed with physical examination by a neurologist.

Transplant-related mortality: death from any cause during the first 100 days from autologous graft infusion.

Anti-Mullerian hormone: a hormone produced by the granulosa cells of growing ovarian follicles in females and the testicles in males, whose measure in the serum is considered a marker of ovarian reserve in females.

Figure 1


Use of AHSCT recommended
Benefits of AHSCT uncertain
Use of AHSCT not recommended
Neurological variables
Age (years)
<45
>55[a]
Disease duration, (years)
<10
>20
Focal inflammation
High
Absent
EDSS score
<4.0
>6.0
Cognitive impairment
Absent
Major
Form of MS
Relapsing–remitting
Secondary progressive
Primary progressive
Treatment failure (≥1 HE-DMT + poor prognostic factors, or ≥1 HE-DMT + ≥1 ME-DMT)
or
Highly aggressive MS with poor prognostic factors[b]
If risk of procedure is low
and
EDSS score is increasing despite treatment
and
Clinical or MRI inflammatory activity within past 12 months
Haematological variables
Medical comorbidities
None
Multiple
Infections
None
Active
Performance status
Excellent
Poor
Family planning
Individual satisfied
Individual not satisfied