Autologous Hematopoietic Stem Cell Transplantation in Active Multiple Sclerosis

A Real-world Case Series

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Abstract

Objective
To examine outcomes in people with multiple sclerosis (PwMS) treated with autologous hematopoietic stem cell transplantation (AHSCT) in a real-world setting.

Methods
This was a retrospective cohort study of PwMS treated with AHSCT at 2 centers in London, UK, consecutively between 2012 and 2019 who had ≥6 months of follow-up or died at any time. Primary outcomes were survival free of multiple sclerosis (MS) relapses, MRI new lesions, and worsening of Expanded Disability Status Scale (EDSS) score. Adverse events rates were also examined.

Results
The cohort includes 120 PwMS; 52% had progressive MS (primary or secondary) and 48% had relapsing-remitting MS. At baseline, the median EDSS score was 6.0; 90% of the evaluable cases showed MRI activity in the 12 months preceding AHSCT. Median follow-up after AHSCT was 21 months (range 6–85 months). MS relapse-free survival was 93% at 2 years and 87% at 4 years after AHSCT. No new MRI lesions were detected in 90% of participants at 2 years and in 85% at 4 years. EDSS score progression–free survival (PFS) was 75% at 2 years and 65% at 4 years. Epstein-Barr virus reactivation and monoclonal paraproteinemia were associated with worse PFS. There were 3 transplantation-related deaths within 100 days (2.5%), all after fluid overload and cardiac or respiratory failure.

Conclusions
Efficacy outcomes of AHSCT in this real-world cohort are similar to those reported in more stringently selected clinical trial populations, although the risks may be higher.

Classification of Evidence
This study is rated Class IV because of the uncontrolled, open-label design.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Glossary

AHSCT = autologous hematopoietic stem cell transplantation; **BEAM** = BiCNU (carmustine), etoposide, Ara-C (cytarabine), melphalan; **DMT** = disease-modifying treatment; **EBMT** = European Bone Marrow Transplantation Society; **EDSS** = Expanded Disability Status Scale; **G-CSF** = granulocyte colony-stimulating factor; **HH** = Hammersmith Hospital; **KCH** = Kings College Hospital; **KM** = Kaplan-Meier; **MDT** = multidisciplinary team; **MS** = multiple sclerosis; **NEDA** = no evidence of disease activity; **PBSC** = peripheral blood stem cell; **PPMS** = primary progressive MS; **PwMS** = people with MS; **rATG** = rabbit anti-thymocyte globulin; **RCT** = randomized controlled trial; **RRMS** = relapsing-remitting MS; **SPMS** = secondary progressive MS; **TRM** = treatment-related mortality.

Autologous hematopoietic stem cell transplantation (AHSCT) has increasingly been used in recent years as treatment for multiple sclerosis (MS) and other severe autoimmune diseases, on the basis of the hypothesis that the procedure may reset the immune system and stop the inflammatory attack.[1] Clinical studies have demonstrated profound suppression of MS activity[2-4] and long-term clinical stabilisation.[5] Refinement of patient selection and treatment protocols has reduced treatment-related toxicity and mortality.[6] Clinically based criteria have helped to define the optimal patient profile for whom AHSCT could be considered an appropriate treatment option.[1] A recent position statement from the American Society for Blood and Marrow Transplantation and treatment guidelines from the European Bone Marrow Transplantation Society (EBMT) recommend considering AHSCT in selected people with MS (PwMS).[7,8] Two small randomized controlled trials (RCTs) in relapsing MS provide proof of principle of higher efficacy of AHSCT compared to standard treatment on MRI[9] and clinical outcomes.[10]

The objective of this observational study is to examine clinical efficacy outcomes and adverse events in a cohort of PwMS treated with AHSCT according to standard clinical practice at the 2 lead centers in London, UK. We also investigated the variables associated with the outcomes. Because symptomatic Epstein-Barr virus (EBV) reactivation increases the risk of neurologic sequelae and the monitoring of EBV-associated monoclonal paraprotein after AHSCT has recently been recommended,[11,12] we also examined the relationship between EBV reactivation and monoclonal paraprotein formation in the AHSCT-treated MS cohort. Furthermore, we explored risk factors, including treatment-related morbidity, on efficacy outcomes.

Methods

Patient Selection

Data were collected retrospectively on consecutive PwMS who underwent AHSCT for treatment of MS between February 15, 2012, and January 2019 at Kings College Hospital (KCH) and from April 12, 2016, to January 2019 at Hammersmith Hospital (HH) (London) and had at least 6 months of follow-up or died at any time. All eligible patients were included in the retrospective analysis. Initially (2012–2015), the indication for AHSCT was based on the agreement of at least 2 neurologists and 1 hematologist with expertise in AHSCT that the treatment was in the patient's best interest in

the absence of appropriate treatment alternatives. Eligibility criteria for treatment were formally defined in September 2015 to select patients with a profile consistent with inflammatory active MS and, for relapsing-remitting MS (RRMS), treatment-refractory disease. The treatment inclusion and exclusion criteria for AHSCT that were implemented since September 2015 are summarized in table 1. Eligibility had to be approved by a multidisciplinary team (MDT) comprising neurologists and transplantation hematologists from a number of independent centers in London and vicinity with established or developing expertise in AHSCT for MS. The MDT reviewed the clinical information collected in a referral form and discussed each case to assess eligibility by consensus. For some cases who did not strictly meet all the inclusion criteria but convincingly fulfilled the overall profile of eligibility (table 1), the MDT made the clinical decision to offer AHSCT, documenting the specific basis for the approval. For this study, MRI reports were audited, and in some cases, scans were reviewed to examine any inconsistency. The patient flow, including the reasons for exclusion from treatment and from study analysis, is shown in the *Consolidated Standards of Reporting Trials* diagram (figure 1). The database was locked for analysis in July 2019, and statistical analysis was completed in December 2019.

Standard Protocol Approvals, Registrations, and Patient Consents

All patients signed informed consent forms before initiating the treatment procedure and to give agreement to data collection and analysis. In line with standard practice, all data were also reported to the EBMT registry database.

Treatment Procedure

Patients underwent AHSCT according to the approved protocols at the 2 centers. At KCH, peripheral blood stem cells (PBSCs) were mobilized after administration of cyclophosphamide 4 g/m^2 over 2 days (62 patients) or cyclophosphamide 2 g/m^2 over 1 day (3 patients) after a modification in the protocol in November 2018, with granulocyte colony-stimulating factor (G-CSF; 5 μg/kg SC) for 7 days until leukapheresis. Conditioning was performed with a standard protocol of cyclophosphamide (50 mg/kg for 4 days) and rabbit anti-thymocyte globulin (rATG; 2.5 mg/kg/d for 3 days, total dose 7.5 mg/kg) for in vivo lymphodepletion followed by stem cell infusion. One patient, at the start of the KCH program, was conditioned with a carmustine/etoposide/cytarabine/melphalan regimen plus an

Table 1 Profile of Eligibility for Treatment With AHSCT

Inclusion criteria
Diagnosis of MS according to McDonald criteria[13-15]
For PPMS, the presence of oligoclonal bands in the CSF was required
Age 18–65 y
Disease duration since diagnosis of ≤15 y
EDSS score between 0 and 6.5
"Inflammatory active MS" as defined by ≥1 gadolinium-enhancing (>3 mm) lesion (off steroids for 1 mo) or ≥2 new T2 lesions on MRI within the last 12 mo
Patients with RRMS had to experience treatment failure with at least 1 licensed DMT of high efficacy,[a] defined as evidence of relapse, MRI activity, or EDSS score increase after being on high-efficacy DMT for at least 6 mo
Exclusion criteria
Eligibility for an ethically approved clinical trial in which AHSCT is offered as 1 of the treatment arms
Inability to adequately understand risk and benefits of AHSCT and give written informed consent
Prior treatment with total lymphoid irradiation and AHSCT or allogeneic hematopoietic stem cell transplantation

Abbreviations: AHSCT = autologous hematopoietic stem cell transplantation; DMT = disease-modifying treatment; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; PPMS = primary progressive MS; RRMS = relapsing-remitting MS.
[a] High efficacy DMT: alemtuzumab, mitoxantrone, natalizumab, ocrelizumab.

equivalent dose of rATG (BEAM [BiCNU (carmustine), etoposide, Ara-C (cytarabine), melphalan]-ATG) before stem cell infusion. The median CD34 stem cell dose returned was 7.17×10^6/kg (range $4.0–17.1 \times 10^6$/kg). At HH, PBSCs were mobilized (52 patients) with cyclophosphamide 2 g/m^2 and daily G-CSF (5 µg/kg SC) starting from day +3 from cyclophosphamide until leukapheresis. Transplantation conditioning used cyclophosphamide (50 mg/kg for 4 days) and rATG (2 mg/kg/d, total dose 6 mg/kg in 48 cases or 2.5 mg/kg/d, total dose 7.5 mg/kg in 4 cases after a protocol change in August 2018). One patient was mobilized with cyclophosphamide 1 g/m^2 followed by G-CSF and plerixafor (2 doses) and conditioned with BEAM-ATG due to intolerance of cyclophosphamide. At both centers, the collected product was not CD34 selected or otherwise manipulated ex vivo. The median CD34+ cell dose in the cryopreserved PBSC product was 7.75×10^6/kg (range $2.2–24.3 \times 10^6$/kg). After conditioning and reinfusion of the autologous PBSC product, G-CSF was administered starting from day 7 after AHCST until engraftment to half of the patients from KCH and to all the patients from HH.

Supportive medical treatments (including platelet and packed red cell transfusions, antimicrobial prophylaxis, dietetics, and physiotherapy support) were provided during the inpatient period as per standard institutional protocols. Psychological support was available for all inpatients.

Clinical and MRI Assessments

Clinical assessments were performed according to standard clinical practice at the centers. To qualify as events, relapses had to be confirmed by a clinician and recorded in the case notes. Changes in the Expanded Disability Status Scale (EDSS) scores in the short term before/after AHSCT were evaluated over the 24-month period comprising 12 months before AHSCT to 12 months after treatment. EDSS score progression was defined as an increase in EDSS score by 0.5 point if baseline EDSS score was ≥6 and by 1 point if baseline EDSS score was <6. MRI scans were performed as per local protocols. MRI analysis, including new lesion counts, was based on the neuroradiology clinical reports. Patient underwent the first posttransplantation MRI scan on average 6 months (range 1–13 months) after AHSCT. For analyses requiring rebaselining of MRI, the first posttransplantation MRI as described above was considered the new baseline scan, and post-AHSCT MRI activity was evaluated by comparing the subsequent scans obtained during follow-up with this scan.

Statistics

The database of transplantations and outcomes was built in Microsoft Excel 2016 (Microsoft Corp, Redmond, WA), and statistical analyses were performed with IBM SPSS Statistics version 24.0 (IBM Corp, Armonk, NY). Patient characteristics are presented as medians (with interquartile ranges) for data with nonnormal distribution. Comparisons of baseline characteristics were performed with the Mann-Whitney U test, Fisher exact test, or χ^2 test for trend as appropriate. The changes in EDSS scores between the 12 months preceding treatment and baseline (premobilization) and between baseline and 12 months after AHSCT were calculated. Pretransplantation and posttransplantation relapse rates were compared by a Wilcoxon test for paired data. Time to first relapse and time to first MRI activity were studied by Kaplan-Meier (KM) survival curves and compared between patients with RRMS and progressive MS by the log-rank test. Confirmed disability worsening was defined when the EDSS score changes defined above were confirmed at 6 months and was assessed by KM curves for univariate analysis and by a Cox model for multivariate analysis. The variables included in the analysis were age, sex, progressive vs relapsing MS subtype, total number of previous disease-modifying treatments (DMTs), number high-efficacy DMT, EBV reactivation, time of EBV reactivation, highest EBV copy number, and detection of serum paraprotein (paraproteinemia). The effect of baseline variables on the risk of developing paraproteinemia was studied by a multivariate Cox model.

Data Availability

Any data not published within the article will be shared in anonymized form on request from a qualified investigator.

Results

Pre-AHSCT MS Disease Characteristics

One hundred twenty PwMS were included in the study. Their demographic and clinical features at baseline are presented in

Figure 1 Consolidated Standards of Reporting Trials Diagram of Enrollment in the Study

Patient disposition is shown in the flowchart with information available about the reasons for exclusion from treatment with autologous hematopoietic stem cell transplantation (AHSCT) or from the cohort analysis. DMT = disease-modifying treatment.
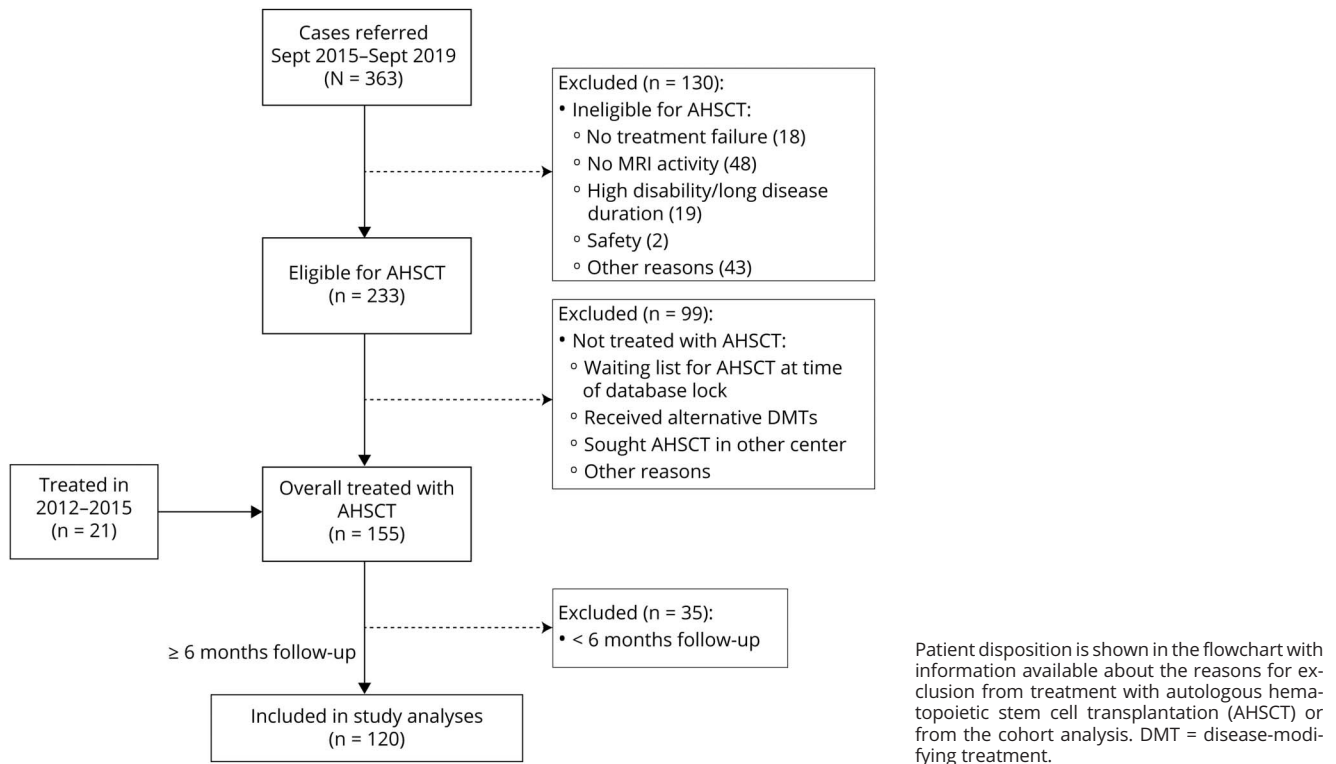
table 2. Sixty-two (52%) cases had a progressive MS phenotype (primary progressive [PPMS] or secondary progressive [SPMS]). At acceptance for AHSCT, 90% of the patients for whom data were available had evidence of MRI activity in the preceding 12 months, demonstrated by new T2 or gadolinium-enhancing lesions (table 2); 85% of the evaluable patients had developed ≥1 T2 lesions, and 59% had a gadolinium-enhancing lesion on MRI.

The cohort had a mean age of 42.3 years and median EDSS score of 6.0. There was no difference in the mean age or EDSS score in the PwMS treated at the 2 centers. Patients with RRMS had received an average of 2.3 previous DMTs (SD 1.3); those with SPMS, 1.6 treatments (SD 1.1). Seventy (58%) patients had been treated before AHSCT with ≥1 DMT regarded as high efficacy (alemtuzumab, mitoxantrone, natalizumab, ocrelizumab), among whom 19 patients had alemtuzumab and 58 had natalizumab (7 had both). The median duration of follow-up after AHSCT, with the autologous graft infusion being day 0, was 21 months (range 6–85 months).

AHSCT Admission and Engraftment
The median duration of hospital inpatient admission was 22 days (mean ± SD 25.3 ± 9.7 days). Median time to neutrophil engraftment was 12 days (mean 12.3 ± 9.2.55 days). There were center differences: the duration of inpatient admission was longer at KCH (median 26 days, mean 27.5 ± 9.7 days)

than at HH (median 20 days, $p = 0.00097$, Wilcoxon test [$w = 2786.5$]; mean 21.7 ± 8.0 days, $p = 0.00052$, t test). The mean time to neutrophil engraftment was also longer at KCH (median 13 days, mean 13.2 ± 2.5 days; 1 missing) than at HH (median 11 days, $p = 0.00072$, Wilcoxon test [$w = 2695.5$]; mean 11.1 ± 2.1 days, $p = 0.0064$, t test; 1 missing).

Neurologic Outcomes After AHSCT

Relapses
The relapse rate in the study population was compared before and after AHSCT. The overall annualized relapse rate dropped from 0.46 ± 0.57 in the 2 years before AHSCT to 0.08 ± 0.38 in the post-AHSCT follow-up at 4 years ($p < 0.001$, Wilcoxon test; figure 2A). Ninety-three percent of all cases were free from relapse at 2 years after AHSCT; 87% were free from relapse at 4 years after AHSCT. Relapses after AHSCT occurred only in patients with RRMS, and in that subgroup, relapse-free survival was 87% at 2 years and 77% at 4 years.

MRI Lesions
Annualized MRI new T2 lesion numbers without rebaselining were compared between the 12 months before AHSCT and the available follow-up of up to 4 years after AHSCT; the last MRI was performed after a mean of 22 months (SD 17.6 months). There was a significant reduction in new T2 lesions after AHSCT in the whole evaluable population ($p < 0.0001$, χ^2 test; figure 2B). At survival analysis, 90% of participants were free of new lesions at 2 years and 85% at 4 years. In

Table 2 Demographics and Disease Characteristics at Baseline

Patient and Disease Characteristics	Evaluable No.	Total Cohort	RRMS	Secondary Progressive MS	PPMS
Disease type, n (%)	120	120 (100)	58 (48)	40 (33)	22 (18)
Female, n (%)	120	58 (48)	33 (57)	19 (47)	6 (27)
Age, mean ± SD, y	120	42.3 ± 8.8	40.2 ± 8.7	43.6 ± 8.4	45.8 ± 8.7
Disease duration since diagnosis, mean ± SD, y	118	8.9 ± 5.3	9.2 ± 6.0	9.8 ± 4.5	6.6 ± 4.1
Baseline EDSS score, median (IQR)	120	6.0 (5.5–6.5)	6.0 (4.0–6.0)	6.5 (6.0–6.5)	6.0 (4.87–6.5)
In the 2 y preceding HSCT: relapse rate, total No. of relapses	116	0.48, 111	0.71, 80	0.36, 29	0.05, 2
Previous treatments, mean ± SD, n	120	1.7 ± 1.4	2.3 ± 1.3	1.6 ± 1.1	0.14 ± 0.3
Patients who tried high-efficacy DMT, n (%)[a]	120	70 (58)	51 (88)	18 (45)	1 (4)
Patients with new T2 lesions, n (%)	103	88 (85)	41 (77)	30 (91)	17 (100)
In the 12 mo preceding HSCT: new T2 lesions, n patients	103	0 lesion: 15 1 lesion: 25 ≥2 lesions: 63	0 lesion: 12 1 lesion: 12 ≥2 lesions: 29	0 lesion: 3 1 lesion: 5 ≥2 lesions: 25	0 lesion: 0 1 lesion: 8 ≥2 lesions: 9
Patients with Gd+ lesions in the preceding year, n (%)	95	56 (59)	26 (58)	16 (53)	14 (70)
Patients with new T2 and/or Gd+ lesions in the preceding year, n (%)	113	102 (90)	46 (84)	34 (94)	22 (100)

Abbreviations: DMT = disease-modifying treatment; Gd+ = gadolinium-enhancing; EDSS = Expanded Disability Status Scale; HSCT = hematopoietic stem cell transplantation; IQR = interquartile range; MS = multiple sclerosis; PPMS = primary progressive MS; RRMS = relapsing-remitting MS.
[a] High-efficacy DMT: alemtuzumab, mitoxantrone, natalizumab, ocrelizumab

contrast to relapses, there was no difference in the development of new T2 lesions between the RRMS and progressive MS subgroups (data not shown).

Neurologic Disability

To first evaluate the short-term evolution of neurologic disability, the change in EDSS scores between 12 months before AHSCT and baseline (premobilization) was compared with the change between baseline and 12 months after AHSCT. In the whole population analysis, the average EDSS score change was 0.25 during the 12 months before AHSCT and 0.02 in the 12 months after therapy (figure 2C). In the subgroup analysis, a clear difference emerged, with patients with RRMS showing on average a small improvement 12 months after AHSCT compared to baseline; in contrast, the progressive MS subgroup showed further deterioration (RRMS subgroup: EDSS score change 0.39 before AHSCT and −0.17 after transplantation; progressive subgroup: 0.11 before AHSCT and 0.24 after AHSCT; $p < 0.05$; figure 2D).
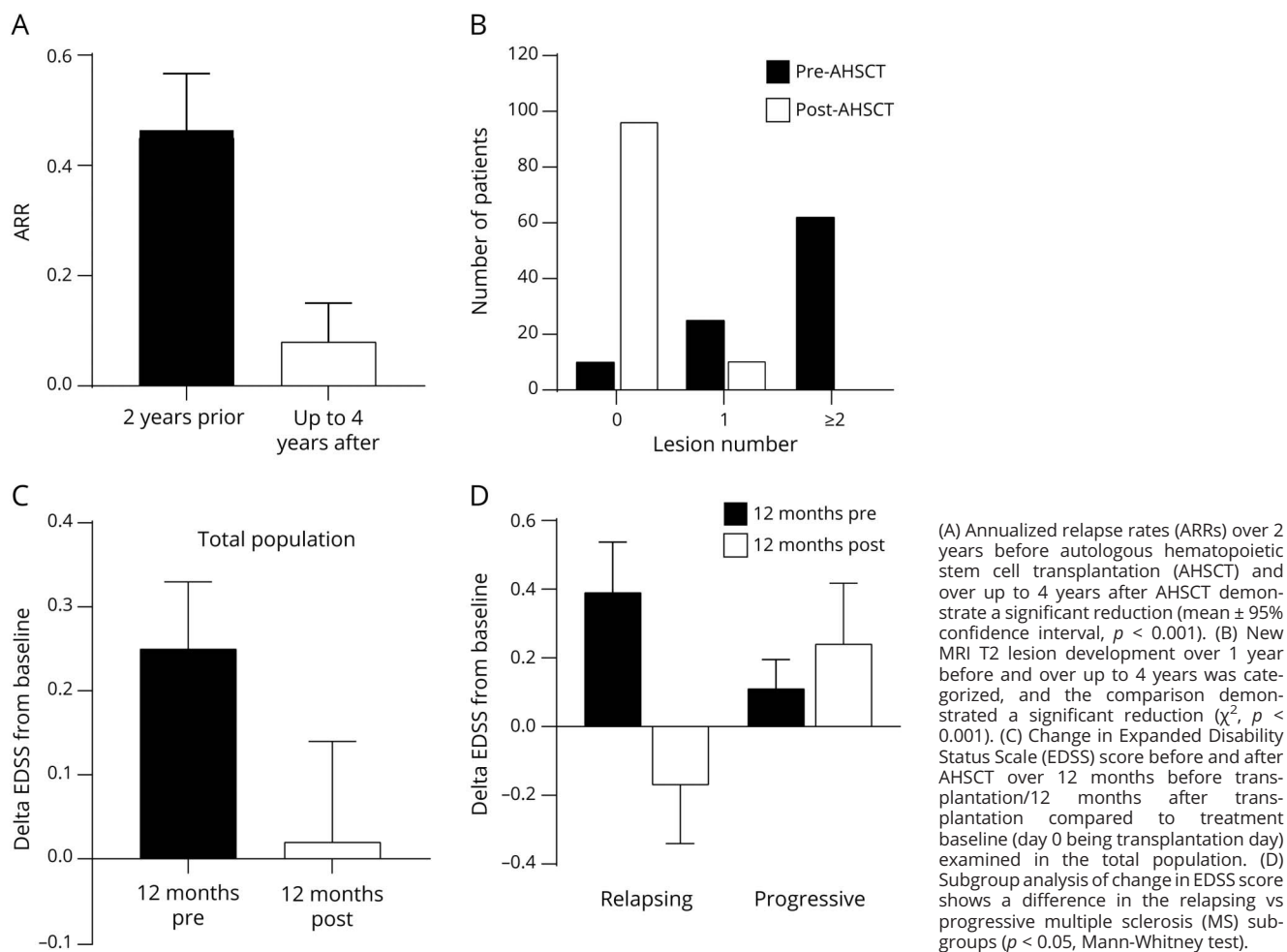
We next examined the evolution of disability in the longer term, assessed as EDSS score worsening confirmed at 6 months or death during the entire follow-up. Seventy-five percent of the whole population did not have confirmed EDSS score worsening at 2 years; the proportion decreased to 65% at the 4-year follow-up. There was no significant difference between the RRMS and progressive MS subgroups ($p = 0.487$, log-rank test; figure 3A). In the RRMS subgroup, 13

participants (including 1 death) had confirmed disability worsening. In the progressive MS subgroup, 15 participants had confirmed disability worsening: 8 with SPMS and 7 (including 2 deaths) with PPMS. Using confirmed EDSS score worsening as an outcome, we explored factors that could predict failure of AHSCT. Demographics, disease phenotype, number and type of previous treatments, and adverse events were included as variables in the analyses. Univariate and multivariate Cox analyses identified high (>5 g/L) paraproteinemia as the only significant variable associated with confirmed EDSS score progression over 4 years (odds ratio 1.07 [95% confidence interval 1.03–1.10], $p < 0.001$; KM plot in figure 3B). Further modeling indicated that paraprotein levels were not predictive of relapses (odds ratio 0.96 [95% confidence interval 0.76–1.20], $p = 0.67$) or new T2 lesions on rebaselined MRI for up to 4 years (0.93 [95% confidence interval 0.72–1.21]).

No Evidence of Disease Activity

No evidence of disease activity (NEDA) has increasingly been used to demonstrate effects of treatment in MS. NEDA fulfilling the 3 endpoints—no relapses, no new MRI lesions, and no worsening of neurologic disability—is denominated NEDA-3. In this study, data enabling calculation of NEDA-3 (without MRI rebaselining) were available for the majority of cases (107 of 120, including the 3 deaths, considered events in the analysis). The survival analysis of NEDA-3 and its components in the whole cohort is shown in figure 3C. The survival

(A) Annualized relapse rates (ARRs) over 2 years before autologous hematopoietic stem cell transplantation (AHSCT) and over up to 4 years after AHSCT demonstrate a significant reduction (mean ± 95% confidence interval, $p < 0.001$). (B) New MRI T2 lesion development over 1 year before and over up to 4 years was categorized, and the comparison demonstrated a significant reduction (χ^2, $p < 0.001$). (C) Change in Expanded Disability Status Scale (EDSS) score before and after AHSCT over 12 months before transplantation/12 months after transplantation compared to treatment baseline (day 0 being transplantation day) examined in the total population. (D) Subgroup analysis of change in EDSS score shows a difference in the relapsing vs progressive multiple sclerosis (MS) subgroups ($p < 0.05$, Mann-Whitney test).

analysis of time to loss of NEDA-3 in the RRMS, SPMS, and PPMS subgroups is presented in figure 3D; the yearly NEDA-3 rates to year 4 after AHSCT are supplied in table 3.

Adverse Events After AHSCT

Early Complications
Almost 90% of the treated patients experienced at least 1 early complication after AHSCT. There were differences in the rates of adverse events between the 2 centers, described in table 4. After mobilization, fever/positive culture/neutropenia and readmission rates were higher in the KCH cohort, possibly related to the higher cyclophosphamide dose (4 g/m^2 vs 2 g/m^2). For conditioning/HSCT, the KCH cohort more frequently experienced fever, diarrhea, and EBV reactivation, whereas severe nausea and vomiting were higher in the HH cohort.

Transplantation-Related Mortality
There were 3 deaths (2.5%) within 100 days from transplantation. Two of the participants had PPMS (1 female and 1 male patient, age at death 58 and 42 years, respectively) and 1 had RRMS (female, age 51 years), and all 3 had an EDSS score

of 6.5 at baseline. Further clinical and treatment details are available from Dryad (table e1, doi.org/10.5061/dryad. k0p2ngf82). Two deaths occurred the day before the planned autologous stem cell infusion; in both cases, the primary cause was cardiac arrest, and secondary causes were recent pulmonary edema in 1 case and blood electrolyte abnormalities in the other. In the third case, death occurred 32 days after stem cells had been reinfused and was caused by acute respiratory distress syndrome secondary to chest infection and sepsis. To investigate the pathophysiologic basis of these events, a detailed retrospective analysis was undertaken in the whole treated cohort. With potential relevance to the mortality events, fluid overload (defined by >5% weight gain ± peripheral or central edema and need for additional diuretics) was recorded in 78 of 118 patients (66%) and presented at a mean of 3 days (±2.2 days SD) after the first dose of ATG. Further data on fluid overload are available from Dryad (table e2).

Viral Reactivations and Paraprotein Formation in the Patient Cohort
Cytomegalovirus reactivation was detected in 26 cases, and preemptive treatment with valganciclovir or ganciclovir was
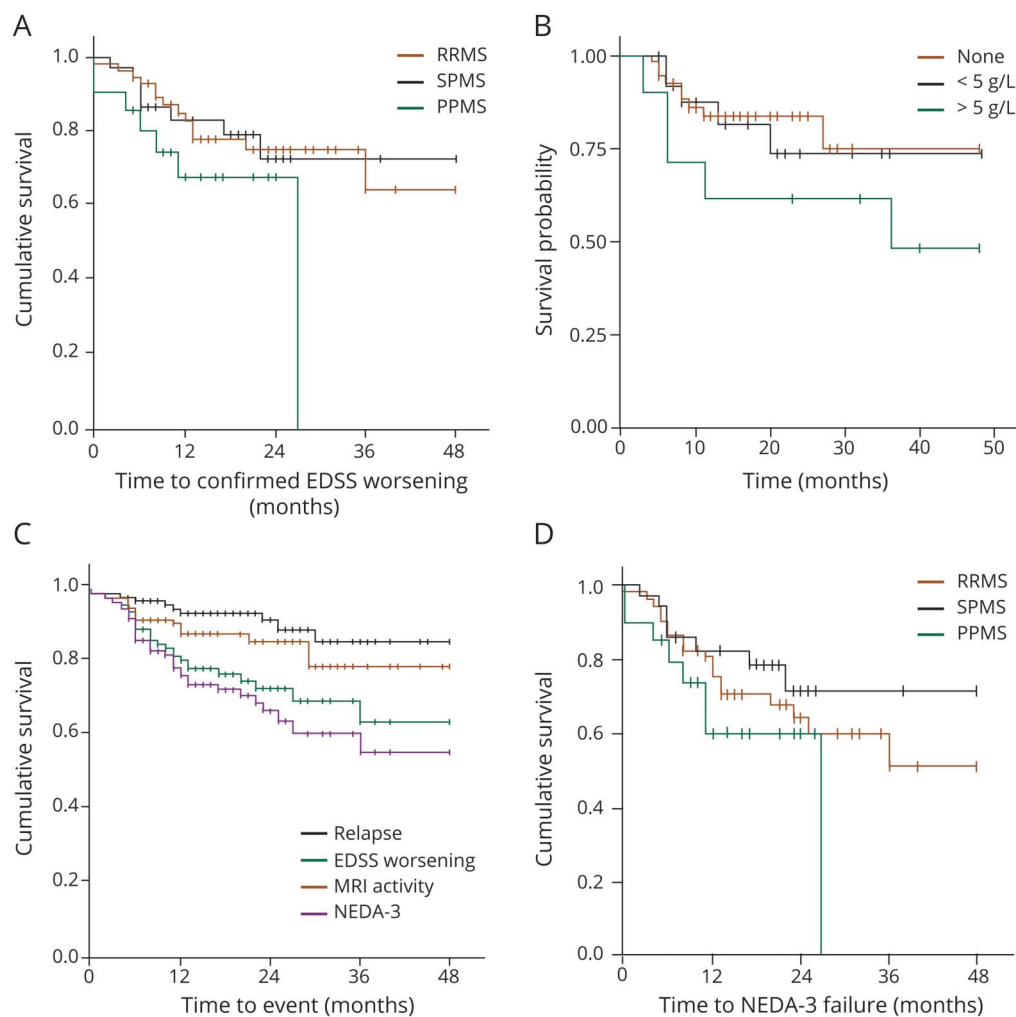
(A) Kaplan-Meier (KM) analysis of time to confirmed Expanded Disability Status Scale (EDSS) score worsening in the relapsing-remitting (RR) multiple sclerosis (MS), secondary progressive MS (SPMS), and primary progressive (PPMS) subtypes. (B) KM of time to confirmed EDSS score worsening according to paraproteinemia (red line, none; green line, <5 g/L; blue line, ≥5 g/L) illustrates the association detected by multivariate analysis (reported in Results). (C) KM of no evidence of disease activity-3 (NEDA-3) and its components: time to relapse, to new T2 MRI lesion, and to confirmed EDSS score progression in the whole population. (D) KM of NEDA-3 in the RRMS, SPMS, and PPMS subgroups.

required in 12 of 26 (46%) cases with no CMV disease observed. EBV serologic status before AHSCT was assessed in a subset of 66 of 120 patients (55%), mainly due to different testing policies in KCH and HH, and was positive in all cases except for 1 indeterminate participant and 1 negative participant. In a subset of 85 participants, EBV DNA copy numbers in blood and paraprotein were measured regularly by standardized laboratory techniques at both sites. EBV reactivation (defined by viremia >10 DNA copies/mL consecutively, as previously described[11]) was demonstrated in 87 of 109 (80%; 11 missing/not tested) of participants after AHSCT. Of the 87 EBV reactivation cases, 20 (23%) cases were treated with rituximab in a median of 4 courses (range 2–4). Hypogammaglobulinemia was detected in 7 of 20 rituximab-treated cases. In a stepwise multivariate Cox analysis, the following variables were associated with risk of developing paraprotein: lower baseline EDSS score ($p =$

0.018), symptoms consistent with viral reactivation ($p = 0.001$), lower EBV DNAemia at the date of first reactivation (<500,000 copies/mL; $p = 0.036$), and peak EBV DNAemia (>500,000 copies/mL; $p = 0.017$). The multivariate analysis is available from Dryad (table e3, doi.org/10.5061/dryad.k0p2ngf82).

Late Adverse Events

Seven patients (5.8%) developed secondary autoimmune diseases (6 thyroiditis and 1 case of autoimmune thrombocytopenia) after a median of 17.5 months (range 6–36 months) after transplantation. One of these patients had previously been treated with alemtuzumab. One patient was diagnosed with melanoma 16 months after AHSCT; this patient had previously received 44 weekly doses of natalizumab. Apart from these individual cases, there was no association of prior DMT with adverse events.

Table 3 NEDA-3 Rates

	Year 1	Year 2	Year 3	Year 4
Whole cohort, %	77	65	59	53
At risk, n	107	67	30	12
RRMS, %	79	63	58	48
At risk, n	52	34	18	7
SPMS, %	82	72	72	72
At risk, n	35	24	10	5
PPMS, %	61	61	20	0
At risk, n	20	9	2	0

Abbreviations: NEDA-3 = no evidence of disease activity-3; PPMS = primary progressive multiple sclerosis; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

Discussion

Increasing evidence supports considering AHSCT as a treatment for patients with aggressive, inflammatory forms of MS.[7,8] Studies in RRMS have demonstrated that AHSCT markedly reduces relapse rates and lesion development and improves disability.[1] Two RCTs have been reported with encouraging results,[9,10] and more definitive RCTs comparing AHSCT with contemporary therapies, including high-efficacy biologicals, are underway. The American Society for Blood and Marrow Transplantation and the EBMT recommend AHSCT as a clinical option for treatment of patients with active relapsing MS, particularly when standard therapy has failed.[7,8] The role of AHSCT is less clear in progressive MS, with poor outcomes in participants with advanced disease,[16,17] although some evidence led to the question of whether, among patients with earlier progressive disease and ongoing inflammatory MS, the rate of progression of disability might be attenuated after therapy.[5] Regarding the safety of AHSCT, current data suggest that the treatment-related risk is higher than with standard DMT but is largely front-loaded as opposed to the poorly understood long-term risk of chronic immune suppression induced by biological therapies, and the risk may be partly offset by higher efficacy against neuroinflammation.[18]

In this study, we report the results of a retrospective analysis of data from 120 patients treated with AHSCT as part of standard care. Different from recent and ongoing clinical trials, our cohort included a substantial proportion (≈50%) of patients with progressive MS, and any type and number of prior treatments were allowed, with the exclusion of total lymphoid irradiation and AHSCT or allogeneic HSCT. Selection of patients who could be offered AHSCT evolved during the survey period and became more restrictive with the introduction in September 2015 of an eligibility profile that included upper limits to age (65 years), disease duration (15

years), and neurologic disability (EDSS score 6.5). The criteria also required evidence of inflammatory disease activity by MRI demonstrating new T2 lesions or the presence of gadolinium enhancement. Even with these refinements, the patient cohort was less stringently selected than in most trials of treatments in MS.

As efficacy outcomes, we examined MS relapses and MRI and EDSS score evolution. Relapses were significantly suppressed after AHSCT compared to before transplantation. In this real-world treated cohort, the relapse-free proportion of individuals with RRMS (≈80% for up to 4 years after HSCT) was not substantially different from those achieved in clinical trials.[4,10,19] In addition, MRI demonstrated almost complete suppression of new lesion development after AHSCT in both the RRMS and progressive MS subgroups. Because persistence or reactivation of MRI would be expected more frequently in patients with RRMS, the results are consistent with a floor effect in both subgroups, reflecting high efficacy of AHSCT against MRI-detectable inflammation in the CNS, as previously demonstrated.[20] In regard to neurologic disability, the clinical relevance of ongoing inflammation in patients with RRMS and its radical suppression after AHSCT are the most plausible reasons for the improvement of neurologic function we observed in the RRMS subgroup after AHSCT, consistent with previous reports.[2,10]

In the longer term, freedom from EDSS score worsening (75% at 2 years and 65% at 4 years) was encouraging, and rates were similar in the RRMS and progressive MS subgroups. This observation does not demonstrate a benefit of AHSCT in patients with progressive MS, but it does suggest a question. After the licensing of DMTs for progressive MS, including ocrelizumab for PPMS and siponimod for SPMS, an RCT could be designed to compare the efficacy, safety, and cost-effectiveness of AHSCT and approved therapy in patients with inflammatory active, progressive MS forms.

We investigated factors associated with progression of EDSS score, and the analysis revealed that high paraproteinemia (≥5 g/L) was a significant factor for EDSS score progression, together with symptomatic EBV reactivation. Particularly in light of the putative association of EBV in the pathogenesis of MS,[21] we speculate that in some patients the reactivation of EBV with high viral loads after AHSCT may predispose and contribute, together with other as-yet unknown susceptibility factors, to continued worsening after treatment.[11] Development of monoclonal paraprotein could be of interest as a marker of immune dysregulation after EBV reactivation, as well as its potential impact on neurologic disability after AHSCT, as also observed in our cohort, and monitoring is now recommended.[11,12]

We examined NEDA, and the rates of 65% at 2 years and 53% at 4 years after AHSCT are slightly below the ranges reported in a pooled analysis of AHSCT trials, in which the proportion of individuals with NEDA was 83.4% (range 70%–92%) at 2 years after AHSCT and 67% (range 59%–70%) at 5 years.[22] Even in our cohort, of whom half were patients with RRMS

Table 4 Side Effects of Mobilization and Conditioning Treatments at the 2 Study Centers

n (%)/mean ± SD[a]	KCH (n = 65)	HH (n = 53)	p Value[b]
Mobilization			
Fever/positive culture, n (%)	3 (4.6)/5 (7.7)	1 (1.9)/0	0.390
Fever or positive culture culture OR neutropenia, n (%)	9 (13.8) 0	1 (1.9) 0	0.019[f]
Diarrhea and vomiting, n (%)	3 (4.6)	4 (7.5)	0.387
Fluid overload, n (%)	1 (1.5)	0	0.551
Neurologic worsening, n (%)[c]	1 (1.5)	2 (3.8)	0.423
Thromboembolism, n	0	0	—
Readmission, n (%)/LOS, d	25 (38)/5.4 ± 2.6	10 (19)/3 ± 1.9	0.016[f]
Conditioning/HSCT			
Fever/positive culture at time of conditioning, n (%)[d]	62 (95.4)/17(26.2)	42 (79.2)/6 (11.3)	0.008[f]/0.074
Fever/positive culture at time of HSCT, n (%)[e]	48 (73.8)/31 (47.7)	45 (84.9)/15 (28.3)	0.216/0.050
Positive culture at time of HSCT Gram positive/Gram negative (both), n (%)	10/23 (2)	5/11 (1)	0.493/0.124 (0.577)
Fever and positive culture and neutropenia at time of conditioning, n (%)	2 (3)	1 (1.8)	0.577
Fever and positive culture and neutropenia at time of HSCT, n (%)	30 (46.1)	15 (28.3)	0.073
Diarrhea, n (%)	52 (80)	31 (58.5)	0.019[f]
Severe nausea/vomiting, n (%)	9 (13.8)	18 (34)	0.018[f]
Fluid overload, n (%)	51 (78.5)	41 (77.4)	0.920
Mucositis, n (%)	21 (32.3)	8 (15.1)	0.052
Rash, n (%)	21 (32.3)	11 (20.8)	0.256
Skin, n (%)	12 (18.5)	8 (15)	0.807
Deranged LFTs, n (%)	5 (7.7)	10 (18.9)	0.124
Neurologic worsening, n (%)[c]	22 (33.8)	20 (37.7)	0.806
Thromboembolism, n (%)	1 (1.5)	4 (7.5)	0.125
ICU admission, n (%)/LOS, d	6 (9)/8.2 ± 8.4	2 (3.7)/11 ± 7.1	0.213
EBV reactivation/not tested, n (%)	58 (89.2)/5	29 (54.7)/4	<0.0001[g]

Abbreviations: EBV = Epstein-Barr virus; HH = Hammersmith Hospital; HSCT = hematopoietic stem cell transplantation; ICU = intensive care unit; KCH = Kings College Hospital; LFT = liver function test; LOS = length of stay; positive culture = blood culture testing positive for pathogens.

[a] Of the 120 cases in the cohort, 2 patients were treated at a different unit within KCH initially, and because no data were available on their inpatient course, they were excluded from this analysis (n = 118).

[b] The p values were calculated with the χ^2/Fisher exact test.

[c] Neurologic worsening was transient and related to fever or sepsis in most cases. Delirium was reported in 2 patients. In 1 patient, the worsening was severe, and a brain MRI was undertaken (uncertain small new lesion).

[d] Conditioning indicates adverse event reported during administration of the conditioning chemotherapy.

[e] HSCT indicates adverse event reported during or after infusion of the autologous peripheral blood stem cell graft (day 0).

[f] $p < 0.05$.

[g] $p < 0.01$.

who had failed previous treatments that included high-efficacy biologics, the year 2 NEDA rate of 65% was better than that of any other DMT, among which even the most effective did not exceed 50%.[1] Of course, these are indirect comparisons and should be used only to generate hypotheses.

In the study cohort, 3 deaths were recorded, which were treatment related and constitute a higher treatment-related mortality (TRM) than reported in recent case series and in any published report that included only patients with RRMS. Two of the patients who died had PPMS; all 3 were at the upper limit of allowed disability with an EDSS score of 6.5, were middle-aged (42, 51, and 58 years), and had comorbid conditions, although minor. All 3 received the same cyclophosphamide conditioning regimen, with some variation of ATG dosage, as shown in data available from Dryad (table

e1, doi.org/10.5061/dryad.k0p2ngf82). Higher baseline EDSS score levels and a lower proportion of cases with RRMS have previously been reported as 2 factors associated with TRM.[6] In the same meta-analysis, older age and the conditioning regimen intensity were also considered and were not confirmed as significant in the multivariate analysis.[22] In a multicenter cohort study of long-term outcomes, higher baseline EDSS score was found to be independently associated with worse overall survival.[23] These associations support the notion that patients with higher EDSS score and progressive MS forms are at higher risk of mortality during and after AHSCT.

In the evaluation of the causes of the 3 deaths in our cohort, cardiac adverse events and fluid overload were identified as factors, even though none of these patients were shown to have any impaired cardiorespiratory function at baseline before AHSCT. Fluid overload is an important side effect of conditioning that has not emerged clearly from earlier studies of AHSCT for MS but has recently been identified in a cancer population as a factor contributing to HSCT outcome.[24] In our cohort of PwMS, a high incidence of clinically significant fluid overload was seen, likely related to the conditioning regimen used with ATG. To put this in context, the incidence was significantly higher compared to a cohort of patients with acquired aplastic anemia (n = 40) at KCH, which is predominantly an autoimmune disorder and in which, after treatment with horse ATG 40 mg/kg/d for 4 days and cyclosporin A (5–mg/kg daily dose), only 22% developed significant fluid overload after ATG ($p < 0.001$) despite the equivalent immunosuppressive and fluid retention properties of treatment with ATG and cyclosporin A and the higher median age (52 years) of the patients with aplastic anemia. The reason for the higher incidence of fluid overload in the MS cohort is unclear. We speculate that previous cardiotoxic DMT (mitoxantrone and cyclophosphamide), use of rATG formulation in the MS AHSCT procedures with added high-dose steroids to reduce risk of ATG reaction, and potentially a subclinical form of neuroautonomic dysfunction in patients with MS might be risk factors. For the last hypothesis, because no significant cardiac comorbid conditions were identified in pretreatment standard organ assessments in this cohort, we suggest that a more detailed cardiac (e.g., cardiac injury biomarker monitoring, stress echocardiogram and/or cardiac MRI for detailed structural and functional assessments) and autonomic evaluations (R-R and tilt test ECG) could help identify PwMS at excess risk. Compared to cancer, any TRM of AHSCT in MS is regarded as less acceptable because, in the majority of patients, untreated or ineffectively treated MS is not immediately life threatening. At the population level, in PwMS, survival is reduced on average by 7 years.[25] However, at an individual level, the reduction in life expectancy could be considerably more severe particularly in those with aggressive forms of MS such as those included in this cohort. In addition, standard therapy is not free from risks, and although the risk in the

short term is almost certainly lower, safety concerns have emerged from longer-term follow-up, prompting withdrawal and limitations of the use of licensed MS therapies.[26,27] Early non-TRM complications such as fever, neutropenia, and diarrhea were common in this AHSCT cohort, as expected. Some of the differences observed in adverse event rates between the 2 centers could be related to the higher ATG dose at KCH (7.5 mg/kg vs 6 mg/kg at HH) where a higher incidence of fever, diarrhea, and EBV reactivation was observed. Among late adverse events, secondary autoimmune disease was observed at a rate similar to the ≈5% reported in a larger multicenter cohort study.[23]

This study has several limitations, including its retrospective design, some variation in treatment protocols, a relatively short follow-up, and lack of a treatment control arm. The heterogeneity of clinical phenotypes, age, disease duration, and EDSS score level is also a challenge in the analysis of outcome data, although such heterogeneity also provides the opportunity to explore AHSCT outcomes in a broader patient population and to examine factors potentially associated with the outcomes, which could not be revealed in the selected populations usually enrolled in clinical trials.

Against the limitations, some important conclusions can be made. The results demonstrate the feasibility of this treatment strategy and provide new information on the potential benefits and risks in a real-world social health care setting. Efficacy outcomes similar to those of clinical trials also can be achieved in real-life patient populations, although risks can be higher, especially in patients with more advanced disease. Furthermore, our study exemplifies a model of service development in the NHS in which innovation can be initiated via MDT collaboration even with minimal funding. Scaling up, long-term sustainability, and optimization of patient pathways, however, require adequate resources.

Disclosure
R.S. Nicholas reports support from advisory boards and travel from Novartis, Roche, and Biogen. He has grant support from the UK MS Society and is a member of a National Institute for Health and Care Excellence Health Technology Assessment Committee. A. Mariottini reports personal fees from Merck-Serono and nonfinancial support from Biogen Idec, Tevan and Novartis. B. Turner has received honoraria and travel grants from and has been a member of advisory boards for Biogen, F. Hoffmann-La Roche Ltd, Merck Serono, Novartis,

Appendix 1 Authors

Name	Location	Contribution
Richard S. Nicholas, PhD	Imperial College London, UK	Designed and conceptualized study; analyzed the data; interpreted the data; drafted the manuscript
Elijah E. Rhone, MD	King's College Hospital, London, UK	Major role in the acquisition of data; analyzed the data; interpreted the data; revised the manuscript for intellectual content
Alice Mariottini, MD	University of Florence, Italy	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Eli Silber, MD	King's College Hospital, London, UK	Acquisition of funding for research; major role in acquisition of data interpreted the data; revised the manuscript for intellectual content
Omar Malik, MD, PhD	Imperial College London, UK	Major role in the acquisition of data; revised the manuscript for intellectual content
Victoria Singh-Curry, MD	Imperial College London, UK	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Ben Turner, MD	Barts Health NHS Trust, London, UK	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
Antonio Scalfari, MD, PhD	Imperial College London, UK	Interpreted the data; revised the manuscript for intellectual content
Olga Ciccarelli, MD, PhD	UCL Queen Square Institute of Neurology, London, UK	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content

Appendix 1 (continued)

Name	Location	Contribution
Maria P. Sormani, PhD	University of Genova, Italy	Analyzed the data; interpreted the data; revised the manuscript for intellectual content
Eduardo Olavarria, MD	Imperial College London, UK	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
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Ian Gabriel, MD	Imperial College London, UK	Major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content
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Appendix 2 Coinvestigators

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Leonora Fisniku, PhD	Brighton and Sussex University Hospitals NHS Trust	Neurologist	Referred patients, contributed to clinical decisions, reviewed patient pathway documents
Ashwini Nandoskar, MD	Imperial NHS Trust, London, UK	Neurologist	Referred patients, contributed to clinical decisions, reviewed patient pathway documents
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Waqar Rashid, PhD	St. George's University Hospital Foundation Trust, London, UK	Neurologist	Referred patients, contributed to clinical decisions, reviewed patient pathway documents

Appendix 2 *(continued)*

Name	Location	Role	Contribution
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Victoria Potter, PhD	Kings Health NHS Trust London, UK	Hematologist	Contributed to clinical decisions, treatment protocols, patient pathway documents, and organization of transplant service
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Matthias Klammer, PhD	St. Georges NHS Trust, London, UK	Hematologist	Contributed to clinical decisions, treatment protocols, patient pathway documents
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Charalampia Kyriakou, PhD	University College Hospitals NHS Trust, London, UK	Hematologist	Contributed to clinical decisions, treatment protocols, patient pathway documents
Brynmor Jones, PhD	Imperial NHS Trust, London, UK	Neuroradiologist	Reviewed imaging and reported scans
Sarah Ware	Kings, London, UK	BMT data coordinator	Contributed to patient pathway documents
Caroline D'Arcy	Imperial NHS Trust, London, UK	MS specialist Nurse	Drafted patient pathway documents

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