Original research

Autologous haematopoietic stem cell transplantation compared with alemtuzumab for relapsing–remitting multiple sclerosis: an observational study

Christina Zhukovsky,1 Sofia Sandgren,2 Thomas Silfverberg,3,4 Sigrun Einarsdottir,5 Andreas Tolf,1 Anne-Marie Landtblom,1 Lenka Novakova,2 Markus Axelsson,2 Clas Malmestrom,2 Honar Cherif,3 Kristina Carlson,3 Jan Lycke,2 Joachim Burman1

ABSTRACT

Objective To compare outcomes after treatment with autologous haematopoietic stem cell transplantation (AHSCST) and alemtuzumab (ALZ) in patients with relapsing–remitting multiple sclerosis.

Methods Patients treated with AHSCST (n=69) received a conditioning regimen of cyclophosphamide (200 mg/kg) and rabbit anti-thymocyte globulin (6.0 mg/kg). Patients treated with ALZ (n=75) received a dose of 60 mg over 5 days, a repeated dose of 36 mg over 3 days after 1 year and then as needed. Follow-up visits with assessment of the expanded disability status scale score, adverse events and MRI investigations were made at least yearly.

Results The Kaplan-Meier estimates of the primary outcome measure ‘no evidence of disease activity’ was 88% for AHSCST and 37% for ALZ at 3 years, p=0.0001. The secondary endpoint of annualised relapse rate was 0.04 for AHSCST and 0.1 for ALZ, p=0.03. At last follow-up, the proportions of patients who improved, were stable or worsened were 57%/41%/1% (AHSCST) and 45%/43%/12% (ALZ), p=0.06. Adverse events grade three or higher were present in 48/69 patients treated with AHSCST and 0/75 treated with ALZ in the first 100 days after treatment initiation. The most common long-term adverse event was thyroid disease with Kaplan-Meier estimates at 3 years of 21% for AHSCST and 46% for ALZ, p=0.005.

Conclusions In this observational cohort study, treatment with AHSCST was associated with a higher likelihood of maintaining ‘no evidence of disease activity’. Adverse events were more frequent with AHSCST in the first 100 days, but thereafter more common in patients treated with ALZ.

INTRODUCTION

Autologous haematopoietic stem cell transplantation (AHSCST) has been used as a therapeutic intervention for multiple sclerosis (MS) since more than twenty years.1 Early reports were encouraging,2,3 and followed by uncontrolled clinical trials.4,5 Some years ago, the report of a phase II randomised controlled trial comparing AHSCST with mitoxantrone was published (ASTIMS),6 suggesting that treatment with AHSCST led to fewer MRI lesions than treatment with mitoxantrone. This was followed by the report of a phase III trial (MIST)7 comparing AHSCST with disease-modifying drugs (DMD) approved by the U.S. Food and Drug Administration (FDA). In the MIST trial, treatment with AHSCST prolonged time to disease progression and increased the likelihood of improvement in disability. One shortcoming of this trial was that only a minority of patients in the control arm were treated with a second generation, highly effective DMD, such as natalizumab. Furthermore, other highly efficacious DMDs, such as alemtuzumab (ALZ) or ocrelizumab, were not available to patients in the control arm. Taken together, current evidence supports AHSCST as a treatment option for patients with relapsing–remitting MS (RRMS) with high clinical and MRI inflammatory disease activity despite the use of one or more approved DMDs.8

ALZ is a highly effective DMD, which was approved by the European Medicines Agency for treatment of RRMS in 2013 and by the FDA the following year. It is superior to treatment with interferon β–1a, with a reduction in relapse rates and reduction of sustained accumulation of disability in the pivotal trials.9,10 Although some concerns regarding safety has limited the use of ALZ, it is still considered one of the most efficacious DMDs presently available for treatment of RRMS. In a recent comprehensive systematic review of all available DMDs, made on the behalf of the American Academy of Neurologists, ALZ came out on top for prevention of relapses as well as disability progression.11 Real-world evidence is generated using data derived from the experience of patients outside of conventional clinical trials and is being increasingly recognised as a complement to randomised controlled trials.12 In this observational study, electronic health records and the Swedish Multiple Sclerosis Register (SMSReg)13 were used to compare efficacy and safety of AHSCST and ALZ using prospectively collected data from two large MS centres employing different treatment algorithms for patients with active RRMS.

METHODS

Study design, setting, and data sources

This was an observational cohort study comparing the outcome and safety of patients with RRMS treated with AHSCST using a cyclophosphamide-based conditioning regimen or ALZ. All patients...
receiving treatment for MS at Uppsala University Hospital or Sahlgrenska University Hospital are recorded in the SMSreg. Patients treated with AHSCT or ALZ from 1 January 2011 to 31 December 2018 were identified through a register search and asked to participate. Patients were followed up at least yearly with expanded disability status scale (EDSS) assessment and MRI. The presence of adverse events was sought at each follow-up visit. Health related data were continuously collected at each follow-up visit and deposited in SMSreg. Data were extracted from SMSreg 30 June 2019 and electronic health records were then scrutinised for accuracy of data and adverse events.

Procedures

AHSCT

Autologous haematopoietic stem cells were mobilised with a single dose of 2 g/m² cyclophosphamide followed by filgrastim 5–10 µg/kg/day for 6–7 days and then harvested approximately 10 days after the start of the mobilisation regimen. No ex vivo graft manipulation was performed. Patients were conditioned with a combination of cyclophosphamide and rabbit antithymocyte globulin (cyclophosphamide 200 mg/kg; rATG 6 mg/kg). Prophylaxis for fungal, viral and bacterial infection was administrated during neutropenia. Prophylaxis for herpes viruses and Pneumocystis jiroveci continued for a minimum of 3 months.

Alemtuzumab

Patients treated with ALZ received a dose of 60 mg over 5 days and a repeated dose of 36 mg over 3 days after 1 year. New courses of 36 mg were administrated if clinical relapses and/or new MRI lesions occurred. An intravenous infusion of 1000 mg methylprednisolone was administered on days 1–3. Aciclovir was given as prophylaxis against herpes virus infection for 1 month after the last ALZ infusion.

Study endpoints

Definition of data points

A clinical relapse was defined as a period of acute worsening of neurological function lasting ≥24 hours not attributable to an external cause such as increased body temperature or acute infection. The annualised relapse rate (ARR) was defined as the number of relapses occurring during a time period divided by the number of years in that time period. Confirmed disability improvement (CDI) was defined as a decrease in EDSS score with at least one point from baseline sustained between two follow-up visits separated in time by no less than 6 months (0.5 points if the baseline EDSS ≥6). Confirmed disability worsening (CDW) was defined as an increase in EDSS score with at least one point from baseline sustained between two follow-up visits separated in time by no less than 6 months (1.5 point if EDSS at baseline was 0, 0.5 points if the baseline EDSS ≥5.5). An MRI event was defined as the appearance of any T2 lesion >3 mm or gadolinium enhancing lesion in the brain or spinal cord not present on the baseline scan. The baseline scan was the last MRI scan made before treatment commenced. No evidence of disease activity (NEDA-3) was defined as absence of clinical relapses, CDW and MRI events.

Primary endpoint

The primary endpoint was the Kaplan-Meier estimate of NEDA-3 at 3 years from the day of haematopoietic stem cell infusion or the day of the first infusion of ALZ.

Secondary endpoints

Secondary endpoints were (1) the Kaplan-Meier estimate of freedom from MRI events, (2) the Kaplan-Meier estimate of freedom from clinical relapses, (3) the Kaplan-Meier estimate of freedom from CDW; (4) the ARR after treatment, (5) the proportion of patients (EDSS ≥2) with CDI/stability/CDW, (6) the EDSS change between baseline and follow-up at one, two and 3 years, (7) adverse events of grade 3 or higher according to Common Terminology Criteria for Adverse Events (CTCAE), V.5.015 within the first 100 days after treatment (expected adverse events from AHSCT, such as neutropenia were excluded from this analysis) and (8) late adverse events after treatment, defined as autoimmune or infectious adverse events grade 2 or higher, or any adverse events grade 3 or higher present at 100 days from treatment or occurring thereafter.

Exploratory analyses

A new baseline was set 1 year after treatment initiation. Then, the Kaplan-Meier estimates of NEDA-3, freedom from MRI events, relapses and CDW at 3 years from the new baseline were used as exploratory endpoints.

Statistical analysis

Statistical analyses were performed with R V.3.5.3 (using the packages: ggplot2, survival, fBasics, ggpubr, moments, survminer, plotrix, grid, gridExtra, lattice and devtools). Data were summarised using frequencies for categorical variables, medians (IQR) for discrete variables and means (±SD) for continuous variables. To determine statistically significant differences between two groups, the χ² test, Student’s t test and the Mann-Whitney tests were used. Survival was estimated using Kaplan-Meier plots (95% CI) and the log-rank test was used.

Table 1 Demographical and clinical data at baseline

| Centre (n) | AHSCT (n=69) | ALZ (n=75) | P value |
|------------|--------------|------------|---------|
| Uppsala/Sahlgrenska | 60/9 | 4/71 | <0.0001*** |
| Sex (n) | | | |
| Men/women | 20/49 | 33/42 | 0.09*** |
| Age (years) | 30 (IQR 26–37) | 35 (IQR 30–41) | 0.005* |
| Disease duration (years) | 6.4 (±s.7) | 7.0 (±s.4) | 0.5* |
| Number of previous treatments (n) | 2 (IQR 1–3) | 2 (IQR 1–3) | 0.8** |
| Treatment naïve | 8 | 11 | |
| Dimethylfumarate | 8 | 9 | |
| Glatiramer acetate | 13 | 5 | |
| Interferon beta | 37 | 36 | |
| IVIG | 4 | 1 | |
| Teriflunomide | 2 | 4 | |
| Cladribine | 0 | 1 | |
| Fingolimod | 15 | 32 | |
| Mitoxantrone | 2 | 1 | |
| Natalizumab | 33 | 57 | |
| Rituximab | 17 | 3 | |
| ARR 1 year prior to treatment | 1.4 (±1.2) | 0.54 (±0.81) | <0.0001* |
| Baseline EDSS | 3 (IQR 2–4) | 2 (IQR 1–2.5) | <0.0001** |
| Baseline ARMSSS | 6.1 (IQR 4.2–7.3) | 4.1 (2.0–5.5) | <0.0001** |

*Student’s t-test, **Mann-Whitney’s test, ***χ² test.
AHSCT, autologous haematopoietic stem cell transplantation; ALZ, alemtuzumab; ARMSSS, age-related multiple sclerosis severity score; ARR, annualised relapse rate.
AHSCT and ALZ are shown in Table 1 and online supplemental patient (1.4%) treated with AHSCT switched to dimethyl fumarate; patients treated with ALZ (4.0%) switched to AHSCT; and one patients treated with ALZ (8.0%) switched to rituximab; three patients treated with ALZ, alemtuzumab.

Worsening. AHSCT, autologous haematopoietic stem cell transplantation; ALZ, alemtuzumab.

RESULTS
Patient characteristics
In total, 147 patients were considered for the study. One patient did not meet the inclusion criteria, since he was treated with AHSCST using an alternative conditioning regimen, another patient was lost to follow-up, the remaining 145 were included, their characteristics summarised in Table 1. A summary of events occurring after therapeutic intervention is shown in Figure 1. Patients treated with AHSCST received 19 (IQR 18–20) days of inpatient care. Engraftment occurred on day +12 (IQR 10–13). All ALZ treated patients received at least one dose, 72 received two doses and 17 received three or more doses of ALZ. During follow-up, four patients treated with AHSCST (5.8%) and six patients treated with ALZ (8.0%) switched to rituximab; three patients treated with ALZ (4.0%) switched to AHSCST; and one patient (1.4%) treated with AHSCST switched to dimethyl fumarate. A summary of treatments given prior to treatment with AHSCST and ALZ are shown in Table 1 and online supplemental figure 1.

Primary endpoint
The Kaplan–Meier estimate of NEDA-3 at 3 years was 88% (95% CI 80% to 97%) for AHSCST and 37% (95% CI 26% to 52%) for ALZ, p <0.0001 (Figure 2A, Table 2).

Secondary endpoints
Efficacy
The Kaplan–Meier estimates for MRI event free survival, relapse-free survival and freedom from CDW are shown in Figure 2B-D and Table 2. The ARR post-AHSCST was 0.04 ±0.2 and 0.1 ±0.3 after initiation of ALZ. At last follow-up, the proportions of patients with CDI/stability/CDW were 58%/40%/1% in patients treated with AHSCST and 45%/43%/12% in patients treated with ALZ, p=0.06. The median EDSS changes at 1, 2 and 3 years after treatment initiation are shown in Table 2.

Early adverse events
During the first 100 days after therapeutic intervention, none of the patients treated with ALZ developed CTCAE grade 3 or higher. In the AHSCST treated group, 48/69 patients developed grade 3 adverse events or higher. Febrile neutropenia was by far the most common grade three adverse event (58%) and was managed with intravenous antibiotics, antipyretics and fluid therapy without any long-term morbidity. Two patients had a grade 4 adverse event. One developed septic febrile neutropenia with hypotonia and EBV reactivation and was observed in the intensive care unit <24 hours but did not require vasopressor treatment nor treatment for EBV reactivation. The other patient developed fever with altered mental status and septic febrile neutropenia requiring intravenous steroids, antipyretics and intravenous broad-spectrum antibiotics, but responded swiftly to treatment. Thirteen patients had grade 3 hypokalaemia. Twelve of them were due to treatment with furosemide during conditioning. Two patients experienced cardiac adverse events; one with atrial fibrillation and one case of pericarditis following cyclophosphamide conditioning. Notably, there was no case of invasive fungal infection, haemorrhagic cystitis or haemophagocytic lymphohistiocytosis. Furthermore, no CMV or EBV reactivation requiring intervention. For a full account of the acute adverse events, see online supplemental Table 1.

Late adverse events
Grade 3 adverse events occurred in five patients (6.7%) in the ALZ group and in one patient (1.4%) in the AHSCST group. The most common grade 3 adverse event was immune mediated thrombocytopenia (n=4, ALZ). Other grade 3 adverse events were breast cancer (n=1, ALZ) and Lyme neuroborreliosis (n=1, AHSCST). Autoimmune adverse events occurred in 35 patients (47%) in the ALZ group and in 14 patients (20%) in the AHSCST group. The most common autoimmune adverse event in both groups was thyroid disease; in total, 31 cases (41%) in the ALZ group and 13 cases (19%) in the AHSCST group. The Kaplan–Meier estimates of thyroid disease at 3 years were 21% for AHSCST and 46% for ALZ, p=0.005 (Figure 3). The most prevalent late infection was herpes zoster, occurring in five patients (6.7%) in the ALZ group and in four patients (5.8%) in the AHSCST group. There was no early or late mortality in either group. For a full account of late adverse events, see online supplemental Table 2.

Exploratory analyses
After rebaseline, the Kaplan–Meier estimates of NEDA, relapse-free survival and freedom from CDW at 3 years were still higher to establish statistically significant differences between survival curves. A p value of <0.05 was considered significant.
with AHSCT than ALZ, whereas the Kaplan-Meier estimates of MRI event-free survival were similar between the groups (online supplemental figure 2 and table 2).

**DISCUSSION**

In this observational cohort study, we compared how two different treatment strategies for patients with RRMS affected outcome. Patients treated with AHSCT were more likely to achieve ‘no evidence of disease activity’ than patients treated with ALZ. As expected, the number of adverse events during the first 100 days after treatment initiation was high in the AHSCT group. These adverse events were manageable and did not result in any recorded long-term morbidity. In contrast, patients treated with ALZ had no serious adverse events related to the infusion of ALZ, but long-term adverse events were about twice as common.

In the study, we exploited differences in local treatment traditions at two major MS centres. At Uppsala University Hospital, AHSCT was predominantly used for active and aggressive MS, whereas ALZ was only used when AHSCT was considered to be inappropriate (e.g., allergy to rabbit proteins) or at the specific request of patients. At Sahlgrenska University Hospital opposite conditions prevailed. Thus, treatment selection was mainly influenced by geographical location and not disease characteristics of the patients, minimising channelling bias. Nevertheless, some disparities between the groups were identified. AHSCT treated patients were on average younger, had more relapses, higher EDSS and age-related MS severity score at baseline, consistent with a more advanced and active disease. Highly active disease was associated with a lower probability of remaining in NEDA-3 despite treatment with natalizumab in the AFFIRM trial and daclizumab in the SELECT trial, whereas no such association could be demonstrated after treatment with cladribine in the CLARITY trial. Such baseline variation may have led to a slight underestimation in the magnitude of the difference in NEDA-3 in the present study. The use of prospectively entered register data and electronic health records ensured the veracity of data, although the analysis was made retrospectively.

NEDA-3 was 37% at 3 years in the ALZ group, similar to the 32%–39% at 2 years that was reported in the CARE-MS I and II trials. The rate of progression was also comparable to the CARE-MS trials. The ARR was 0.12 in the ALZ group, arguably a little lower than the 0.18–0.26 in CARE-MS I and II and the 0.16–0.21 in years 3–5 in the extension studies of CARE-MS I and II. However, the baseline ARR was also lower in the present study than in the CARE-MS studies and the relative decrease in ARR was quite similar. A larger proportion of patients improved in EDSS after ALZ treatment than in CARE-MS II (29%/ 54%/16%) and the follow-up extension study over 3 years (25%/52%/23%), perhaps reflecting the presence of a run-in period when ALZ is used in clinical practice. The proportion of patients with NEDA-3 after AHSCT (88%) at

**Table 2** Follow-up data

|                          | AHSCT (n=69) | ALZ (n=75) | P value |
|--------------------------|-------------|------------|---------|
| Total number of follow-up years | 195         | 217        |         |
| Follow-up time per patient (years) | 2.8 (±1.6) | 2.9 (±1.1) | 0.8*    |
| ARR post-treatment        | 0.04 (±0.2) | 0.1 (±0.3) | 0.03**  |
| ΔEDSS after treatment     |             |            |         |
| 1 years                   | −1 (IQR −1.5 to 0) | 0 (IQR −0.5 to 1.3) | <0.0001** |
| 2 years                   | −1 (IQR −2 to −0.5) | 0 (IQR −0.5 to 0.5) | <0.0001** |
| 3 years                   | −1 (IQR −2.5 to −0.5) | 0 (IQR −0.5 to 1) | <0.0001** |

Kaplan-Meier estimates at 3 years

|                           | AHSCT (n=69) | ALZ (n=75) | P value |
|---------------------------|-------------|------------|---------|
| NEDA-3                    | 88% (95% CI 80% to 97%) | 37% (95% CI 26% to 52%) | <0.0001**** |
| Freedom from MRI events   | 93% (95% CI 86% to 99%) | 55% (95% CI 44% to 69%) | <0.0001**** |
| Freedom from clinical relapses | 93% (95% CI 86% to 100%) | 70% (95% CI 59% to 83%) | 0.005**** |
| Freedom from CDW          | 97% (95% CI 93% to 100%) | 82% (95% CI 73% to 92%) | 0.02**** |

Kaplan-Meier estimates after rebaseline

|                           | AHSCT (n=69) | ALZ (n=75) | P value |
|---------------------------|-------------|------------|---------|
| NEDA-3                    | 77% (95% CI 61% to 98%) | 49% (95% CI 32% to 75%) | 0.003**** |
| Freedom from MRI events   | 78% (95% CI 62% to 98%) | 78% (95% CI 65% to 93%) | 0.5**** |
| Freedom from clinical relapses | 96% (95% CI 90% to 100%) | 70% (95% CI 53% to 94%) | 0.04**** |
| Freedom from CDW          | 100% (95% CI 100% to 100%) | 83% (95% CI 71% to 97%) | 0.006**** |

*Student’s t-test, **Mann-Whitney’s test, ***χ² test, ****Log-rank test.

AHSCT, autologous haematopoietic stem cell transplantation; ALZ, alemtuzumab; ARR, annualised relapse rate; CDW, confirmed disability worsening; EDSS, expanded disability status scale; NEDA, no evidence of disease activity.

Figure 3 Thyroid disease. Patients treated with alemtuzumab (ALZ) were more likely to develop thyroid disease than patients treated with autologous haematopoietic stem cell transplantation (AHSCT; log rank test, p=0.0055).
in a Swedish survey, 78% at 2 years and 68% at 5 years;24 and in the MIST trial, 93% at 2 years and 79% at 5 years.2 The ARR of 0.04 post-AHSCT was very similar to the 0.03 that was reported in the Swedish survey.24 The proportion of patients with improvement/stable disease/worsening after AHSCT was also similar to the 67%/29%/4%/4% reported in the MIST study.25

Recently, the results of a real-life single-centre study comparing the outcome of patients treated with AHSCT or ALZ was reported.26 Although a different conditioning regimen was used (consisting of BCNU, etoposide, cytosine-arabinoside, melphalan and rATG), the results were comparable to those in the present study, with a Kaplan-Meier estimate of NEDA-3 of 75% for AHSCT and 56% for ALZ, an ARR of 0.05 for AHSCT and 0.35 for ALZ after treatment initiation and an association with improved outcome in EDSS for AHSCT.

In recognition of the fact that full effect of ALZ treatment may take up to 1 year, an ancillary analysis of the primary endpoint and some of the secondary endpoints was made after a new baseline was set, 1 year after the initiation of treatment. After rebaseline, the Kaplan-Meier estimate of NEDA-3 for ALZ increased from 37% to 57% and for AHSCT decreased somewhat from 88% to 77%, but the difference between AHSCT and ALZ remained substantial and statistically significant. Patient-reported outcome measures, such as quality of life, would have been a valuable addition to the study, but these had not been collected systematically.

In this study, there were no late adverse events of grade 4 (life-threatening conditions in need of urgent intervention) or grade 5 (death). Early toxicity after AHSCT occurred to the expected degree and was manageable with standard medical care. No serious or unexpected adverse events of ALZ infusions were recorded. Late adverse events of ALZ and AHSCT have been described after treatment of MS, including both infectious and autoimmune complications as well as treatment-related mortality.26-31 Late adverse events of grade 3 or higher were uncommon in both cohorts. Nearly half of the patients treated with ALZ had an autoimmune adverse event, compared with 20% in the AHSCT group; this constitutes the major difference in the late adverse events between the groups. The frequency and distribution of thyroid malfunctions following ALZ is well described after treatment of MS, including both infectious and autoimmune complications as well as treatment-related mortality, while

The main limitation of this study is the non-randomised intervention. Therefore, the findings should be confirmed in a randomised controlled trial and at least one is presently underway (ClinicalTrials.gov Id: NCT03477500). Meanwhile, patients who are willing to accept the predictable side effects of AHSCT and the increased risk of short-term adverse events in a one-time procedure might be better off with AHSCT, while patients who prefer a more convenient treatment that can be administered in an outpatient setting are probably better served by ALZ.

Contributors JB and JL planned the study, SE, HC and KC were part of the team that performed AHSCT, AT, AM-L and JB worked at the MS clinic in Uppsala and SS, LN, MA, CM and JL worked at the MS clinic in Gothenburg. TS and AT collected safety follow-up data in Uppsala. CZ collected efficacy follow-up data in Uppsala. SE and SS collected safety follow-up data in Gothenburg. SS collected efficacy follow-up data in Gothenburg, TS, AT and JB analysed safety data. CZ and JB analysed efficacy data. CZ, TS, AT and JB wrote the draft. All authors provided creative input to the final manuscript.

Funding This study was funded by the Swedish Society for Medicine (SSL-726341), the Swedish Society for Medical Research, the Swedish Multiple Sclerosis Research Foundation, the Swedish Federal Government (LUV/ALF Agreement ALFGBG-722081), the Swedish Association of Persons with Neurological Disabilities, the Research Foundation of the Multiple Sclerosis Society of Gothenburg, the Edith Jacobson Foundation, and NEURO Sweden.

Competing interests AM-L has received compensation for lectures and/or service on advisory boards Roche, Sanofi, Merck Serono, Biogen and Teva. LN has received lecture honoraria from Biogen and Novartis and served on advisory boards for Merck. CM has received compensation for lectures, service on advisory boards and/or travel expenses from Sanofi-Genzyme, Merck, Novartis and Roche. MA has received compensation for lectures and/or service on advisory boards from Biogen, Genzyme, and Novartis. JL has received travel support and/or lecture honoraria from Biogen, Novartis, Merck, Alexion, Roche and Sanofi/Genzyme; has served on scientific advisory boards for Biogen, Novartis, Merck, Roche, BSM and Sanofi/Genzyme; serves on the editorial board of the Acta Neurologica Scandinavica; has received unconditional research grants from Biogen, and Novartis.

Patient consent for publication Not required.

Ethics approval The study was approved by the Regional Ethical Board of Uppsala (Dnr 2012/080/1), Stockholm (Dnr 2017/32-31/4) and Gothenburg (reference number 460-13). All patients provided informed and written consent in accordance with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Anonymised data are available upon request.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Andreas Tolf http://orcid.org/0000-0002-0580-8821
Joachim Burman http://orcid.org/0000-0002-7045-1806

REFERENCES
1 Fassas A, Anagnostopoulos A, Kaisis A, et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first results of a pilot study. Bone Marrow Transplant 1997;20:631–8.
Multiple sclerosis

2. Fagius J, Lundgren J, Öberg G. Early highly aggressive MS successfully treated by hematopoietic stem cell transplantation. *Mult Scler* 2009;15:229–37.

3. Burt RK, Loh Y, Cohen B, et al. Autologous non-myeloablative haematopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase III study. *The Lancet Neurology* 2009;8:244–53.

4. Nash RA, Hutton GJ, Racke MK, et al. High-Dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): a 3-year interim report. *JAMA Neurol* 2015;72:159–69.

5. Atkins HL, Bowman M, Allan D, et al. Immunoadabation and autologous haematopoetic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. *Lancet* 2016;388:376–85.

6. Mancardi GL, Sormani MP, Guandalini S, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. *Neurology* 2015;84:98–114.

7. Burt RK, Balabanov R, Burman J, et al. Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial. *JAMA Neurol* 2019;86:165–74.

8. Sharrack B, Saccardi R, Alexander T, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT autoimmune diseases Working Party (ADWP) and the joint accreditation Committee of EBMT and ISCT (JACIE). *Bone Marrow Transplant* 2020;55:283–306.

9. Cohen JA, Coles AJ, Arnold DL, et al. Alemtuzumab versus interferon beta 1A as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012;380:1819–28.

10. Coles AJ, Tbyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012;380:1829–39.

11. Rae-Grant A, Day GS, Marrie RA, et al. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018;90:789–800.

12. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence - What Is It and What Can It Tell Us? *N Engl J Med* 2016;375:2293–7.

13. Hillert J, Stawiarz L. The Swedish MS registry – clinical support tool and scientific resource. *Acta Neurol Scand* 2015;132:11–19.

14. Kurtze JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–52.

15. Common terminology criteria for adverse events V. 5.0: Available: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf [Accessed 15 Apr 2020].

16. Manouchehri A, Westerling H, Kingswell E, et al. Age related multiple sclerosis severity score: disability ranked by age. *Mult Scler* 2017;23:1938–46.

17. Havrdova E, Galetta S, Hutchinson M, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the natalizumab safety and efficacy in relapsing-remitting multiple sclerosis (affirm) study. *Lancet Neurol* 2009;8:254–60.

18. Havrdova E, Giovannoni G, Stefosi D, et al. Disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with daclizumab high-yield process in the select study. *Mult Scler* 2014;20:464–70.

19. Giovannoni G, Cook S, Rammohan K, et al. Sustained disease-activity-free status in patients with relapsing-remitting multiple sclerosis treated with cladribine tablets in the clarity study: a post-hoc and subgroup analysis. *Lancet Neurol* 2011;10:329–37.

20. Coles AJ, Cohen JA, Fox EJ, et al. Alemtuzumab CARE-MS II 5-year follow-up: efficacy and safety findings. *Neurology* 2017;89:1117–26.

21. Havrdova E, Arnold DL, Cohen JA, et al. Alemtuzumab CARE-MS I 5-year follow-up: durable efficacy in the absence of continuous MS therapy. *Neurology* 2017;89:1107–16.

22. Giovannoni G, Cohen JA, Coles AJ, et al. Alemtuzumab improves preexisting disability in active relapsing-remitting MS patients. *Neurology* 2016;87:1985–92.

23. Nash RA, Hutton GJ, Racke MK, et al. High-Dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. *Neurology* 2017;88:842–52.

24. Burman J, Iacobaeus E, Svenningsson A, et al. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. *J Neurol Neurosurg Psychiatry* 2014;85:1116–21.

25. Boffa G, Lapucci C, Sbragia E, et al. Aggressive multiple sclerosis: a single-centre, real-world treatment experience with autologous haematopoietic stem cell transplantation and alemtuzumab. *Eur J Neurol* 2020;3:409.

26. Tuohy O, Costelloe L, Hill-Cawthorne G, et al. Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy. *J Neurol Neurosurg Psychiatry* 2015;86:208–15.

27. Holmøy T, Fevang B, Olsen DB, et al. Adverse events with fatal outcome associated with alemtuzumab treatment in multiple sclerosis. *BMC Res Notes* 2019;12:497.

28. Frau J, Coghe G, Loreffe I, et al. Efficacy and safety of alemtuzumab in a real-life cohort of patients with multiple sclerosis. *J Neurol* 2019;266:1405–11.

29. Scappaticcio L, Castellana M, Virili C, et al. Alemtuzumab-induced thyroid events in multiple sclerosis: a systematic review and meta-analysis. *J Endocr Invest* 2020;43:219–29.

30. Loh Y, Oyama Y, Statkute L, et al. Development of a secondary autoimmune disorder after hematopoietic stem cell transplantation for autoimmune diseases: role of conditioning regimen used. *Blood* 2007;109:2543–54.

31. Muraro PA, Pasquini M, Atkins HL, et al. Long-Term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. *JAMA Neurol* 2017;74:459–69.

32. Burman J, Tolf A, Hägglund H, et al. Autologous haematopoietic stem cell transplantation for neurological diseases. *J Neurol Neurosurg Psychiatry* 2018;89:147–55.

33. Tramacere I, Del Giovane C, Salvati G, et al. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *Cochrane Database Syst Rev* 2015:CD011381.