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Kalincik, T. orcid.org/0000-0003-3778-1376, Sharmin, S., Roos, I. orcid.org/0000-0003-0371-3666 et al. (46 more authors) (2025) Haematopoietic stem cell transplant versus immune-reconstitution therapy in relapsing multiple sclerosis. Brain. awaf286. ISSN: 0006-8950

https://doi.org/10.1093/brain/awaf286

Haematopoietic stem cell transplant versus immune-reconstitution therapy in relapsing multiple sclerosis

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Abstract

In the treatment of relapsing-remitting multiple sclerosis, autologous hematopoietic stem cell transplant and immune-reconstitution therapies show several similarities. These treatment strategies have not yet been compared head-to-head. This study emulated pairwise trials of comparative effectiveness of stem cell transplant vs. immune-reconstitution therapies cladribine and alemtuzumab.

This cohort/registry study of comparative treatment effectiveness included data from 7 specialist multiple sclerosis centres with autologous hematopoietic stem cell programs (RESCUE-MS) and international MSBase registry during 2006-2023. The study included patients with relapsing-remitting multiple sclerosis treated with autologous hematopoietic stem cell transplant, cladribine or alemtuzumab, with a minimum of 2-month follow-up before commencing study therapy and

≥2 disability assessments after commencing the study therapy. Patients were matched on a propensity score derived from their clinical and demographic characteristics. The matched groups were compared on annualised relapse rates freedom from relapses and 6-month confirmed disability worsening and improvement (measured with Expanded Disability Status Scale).

The matching of 143 (stem cell) to 283 cladribine-treated patients and of 134 (stem cell) to 562 alemtuzumab-treated patients reduced the measured differences between the groups by 98% and 96%, respectively. The matched patients had high mean disease activity (>0.8 relapses in the prior 2 years), mean Expanded Disability Status Scale scores of 3-4, and were followed-up for a mean of 3.8-3.9 (stem cell), 1.9 (cladribine) or 4.5 years (alemtuzumab). Compared to cladribine, stem cell transplant was associated with a lower risk of relapses (mean annualised relapse rate ± standard deviation 0.05±0.28 vs. 0.16±0.39, respectively; hazard ratio 0.24, 95% confidence interval 0.15-0.41), similar risk of disability worsening (hazard ratio 0.70, 95% confidence interval 0.34-1.43) and higher probability of disability improvement (hazard ratio 2.19, 95% confidence interval 1.31-3.66). Compared to alemtuzumab, stem cell transplant was associated with a lower risk of relapses (mean annualised relapse rate ± standard deviation 0.04±0.23 vs. 0.09±0.21, respectively; hazard ratio 0.52, 95% confidence interval 0.29-0.93), similar risk of disability worsening (hazard ratio 0.95, 95% confidence interval 0.53-1.72) and higher probability of disability improvement (hazard ratio 2.03, 95% confidence interval 1.23-3.34). 34% of patients treated with stem cell transplant experienced delayed complications, mainly infections. No treatment-associated deaths were reported.

Among patients with active relapsing-remitting multiple sclerosis and moderate disability, autologous hematopoietic stem cell transplant is superior to cladribine and alemtuzumab at suppressing relapses and enabling recovery of neurological function. The high effectiveness of stem cell transplant is likely attributable to a complex interplay of immune suppression and reconstitution.

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Keywords: stem cells, disease modifying therapy, relapses, disability, propensity score

Running title: Stem cell therapy in multiple sclerosis

Introduction

Ongoing clinical or radiological activity during treatment with high-efficacy disease modifying therapies (DMTs) in relapsing multiple sclerosis (MS) represents a difficult clinical scenario. A joint ECTRIMS and EBMT statement has recommended profound immunodepletion followed by autologous hematopoietic stem cell transplant (AHSCT) as a treatment strategy suitable for people with highly active MS in response to failure of high-efficacy DMTs to control MS relapses.[1] AHSCT induces ablation and subsequent reconstitution of the immune system, eliminating localised, episodic inflammation within the central nervous system over many years.

Single-arm cohort studies reported freedom from relapses and worsening of disability in a considerable proportion of patients with aggressive MS post-AHSCT over 5-10 years.[2-6] For example, in a cohort of 145 participants conditioned with cyclophosphamide in combination with alemtuzumab or anti-thymocyte globulin, a 4-year relapse-free survival was 80%, with half of the

patients experiencing reduction in disability early after AHSCT.[4] Among 48 patients treated with BEAM/anti-thymocyte globulin, a relapse-free survival at 5 years was 87%.[3] Twenty-four patients who were treated with the most potent conditioning regimen of busulfan, cyclophosphamide and anti-thymocyte globulin have remained free from relapses up to 13 years post-AHSCT.[2]

However, AHSCT is associated with significant risks, including complications of immune ablation, infections and febrile neutropenia.[1,7] The risk of treatment-related mortality has declined from 2% to less than 0.3%, in parallel with improved patient selection, transplant centre experience and increased use of less potent conditioning regimens.[8]

High-quality cohorts helped establish that AHSCT offers superior control of disease activity compared to conventional DMTs in relapsing MS but not non-active progressive forms of MS.[9-12] Only one open-label phase 3 randomised trial compared the efficacy of AHSCT with a combination of DMTs and off-label interventions in relapsing-remitting MS.[13] It remains unclear whether the profound and complex effect of AHSCT on the immune system results in a more complete and sustained disease control than the conventional immune-reconstituting DMTs.

In the absence of clinical trial data, we have used a statistical approach to emulate two clinical trials in a large composite dataset.[14,15] The emulated trials compared the effectiveness of AHSCT with two commonly used immune-reconstitution DMTs, cladribine and alemtuzumab.

Materials and methods

Patients and data

Data were recorded prospectively between May 2006 and November 2023 at 7 specialised AHSCT centres (in Ottawa, Uppsala, Sheffield, Bergen, Sydney, Melbourne and Prague – presently involved in the RESCUE-MS collaboration) and 63 centres in 21 countries from the MSBase registry (WHO study registration ACTRN12605000455662). The study was approved by the Melbourne Health Human Research Ethics Committee and the site institutional review boards. Patients provided written informed consent, as required. The data are the property of the

individual centres; they can be requested for replication of this study, at the discretion of each principal investigator. This study is reported following the STROBE guideline.

The inclusion criteria were relapsing-remitting MS,[16-18] first exposure to one of the study therapies, no documented participation in randomised clinical trials within the prior 10 years, minimum recorded follow-up of 2 months prior to treatment start, baseline EDSS (excluding scores recorded within 30 days of a prior relapse), 2 post-baseline disability scores (including ≥1 on treatment), and minimum dataset (consisting of sex, age, date of first MS symptom, date of commencing studied therapy, dates of clinical relapses, clinical MS course, disability score at treatment commencement (-9 months to +1 month)). Patients treated with AHSCT were included consecutively.

A sensitivity analysis was carried out among patients who received their studied therapy after 2010.

Procedures

Patients received AHSCT following protocols specific to the treating centres.[2,3,5,19] Autologous haematopoietic stem cells were mobilised using cyclophosphamide 2-4.5 g/m^2 IV with granulocyte colony stimulating factor 5-10µg/kg. In a small number of patients, the mobilisation used granulocyte colony stimulating factor only or in combination with methylprednisolone. The cells were then harvested by leukapheresis and cryopreserved. In approximately one third of patients, the graft was depleted of mature immune cells with CD34 immunomagnetic selection. The transplant conditioning regimens were commenced >3 weeks after mobilisation and included BEAM (carmustine 300mg/m^2, etoposide 200-800mg/m^2, cytarabine 200mg/m^2 and melphalan 140mg/m^2), busulfan with cyclophosphamide 50mg/kg, or cyclophosphamide 200mg with anti-thymocyte globulin 10mg/kg. Rabbit/horse anti-thymocyte globulin was used in 84% of patients. None of the conditioning regimens included alemtuzumab. Infection prophylaxis was used as per local protocols.

The patients included in the DMT arms were treated either with oral cladribine (in at least two courses of 1.75mg/kg 12 months apart) or intravenous alemtuzumab (in at least two courses of 5 and 3 days, 12 months apart, 12-24mg per day). Baseline was defined as the first day of AHSCT

conditioning or the first dose of studied DMT. Patients were censored at commencing another DMT, or at the last recorded disability score, whichever occurred first. The minimum duration of the effect of the studied therapies was set at 5 years from their commencement.[20]

The analysed data were recorded as part of routine practice, mostly at tertiary MS services, with real-time data entry. The MSBase Study Protocol stipulates minimum annual acquisition of disability scores.[21] Data were recorded in iMed, MSBase Data Entry System or local data repositories. Data from different sources were mapped, combined and underwent a rigorous quality procedure (eTable 1).[22]

Outcomes

The primary endpoint was the on-treatment annualised relapse rate (ARR). A relapse was defined as new symptoms or exacerbation of existing symptoms persisting for ≥24 hours, in the absence of concurrent illness/fever, and occurring ≥30 days after a previous relapse.[23] Confirmation of relapses by Expanded Disability Status Scale (EDSS) was not mandated. ARR was calculated for each patient between baseline and censoring.

Secondary endpoints were the proportions of patients who experienced a post-baseline relapse, disability worsening or disability improvement. Disability was scored prospectively by EDSS raters (Neurostatus certification was required at each site), excluding scores recorded within 30 days following a relapse. Disability worsening was defined as an increase in EDSS by ≥1 step if baseline EDSS was between 1 and 5.5, ≥1.5 steps if baseline EDSS=0, and ≥0.5 steps if baseline EDSS>5.5, confirmed by subsequent EDSS scores over ≥6 months. Disability improvement was defined as a decrease in EDSS by ≥1 step if baseline EDSS was between 2 and 6, 1.5 step if baseline EDSS=1.5 and ≥0.5 steps if baseline EDSS>6, confirmed by subsequent EDSS scores over ≥6 months.[24]

Safety information was recorded systematically in the AHSCT group and included: febrile neutropenia, serum sickness, ICU admission, infectious and other complications after discharge, and mortality.

Statistical analysis

The Statistical Analysis Plan can be accessed at https://osf.io/b3w6p/?view_only=cf31816e9cc14cb681cf0ed05e098a53. This study emulated two clinical trials comparing AHSCT with cladribine and alemtuzumab (eTable 2).[25] Matching and statistical analyses were conducted with R (v4.1.1).[26] Individual patients were matched on their propensity of receiving either of the compared therapies in variable matching ratio (1:10 for cladribine, 1:7 for alemtuzumab) without replacement within a caliper of 0.1 standard deviations of the propensity score. Individual propensity scores were calculated using a multivariable logistic regression of treatment allocation with demographic and clinical information at baseline as independent variables: sex, age, EDSS, number of relapses 12 and 24 months before baseline, time from first symptom of MS to baseline, the most effective prior DMT and geographical region.

All subsequent analyses were designed as paired models with weighting to account for the variable matching ratio (cumulative weight per patient≤1). ARRs were compared with a weighted negative binomial model with cluster effect for matched pairs. The cumulative hazards of first relapse, disability worsening, and disability improvement were evaluated with weighted conditional proportional hazards models (Cox) with robust estimation of variance and adjusted for post-baseline visit frequency for the disability outcomes. The assumption of the proportionality of hazards was evaluated by inspection of cumulative hazard curves and the Schoenfeld's global test.

Robustness of the statistically significant differences to unidentified confounders was quantified with Hodges-Lehmann Γ.[27] For each analysis that did not find evidence of difference between the compared groups, the minimum detectable effect at $\alpha=0.05$ and $1-\beta=0.80$ was estimated with 200 simulations.

Results

A total of 177 (AHSCT), 1147 (cladribine) and 471 (alemtuzumab) patients fulfilling the inclusion criteria were identified (Figure 1, eTable 3). Among the AHSCT cohort, the conditioning was used as follows (eTable 4): high-intensity in 36 patients (20%), intermediate-

intensity myeloablative in 45 patients (25%) and low-intensity lymphoablative in 96 patients (55%).[28] Each patient received one course of conditioning and AHSCT. Most patients in the cladribine group received 2 courses of cladribine, with 37 treated with 3, 9 patients treated with 4, and 1 patient treated with 5 courses. Most patients in the alemtuzumab group received 2 courses of alemtuzumab, with 11 patients treated with 3, and 2 patients treated with 4 courses. As expected, the three groups differed in their baseline characteristics before matching (eTable 5). From the logistic regression models used to derive the propensity scores, it is apparent that patients who commenced AHSCT tended to be younger, with higher disability and more common prior use of high-efficacy therapies than the two studied DMTs (eTable 6). After receiving the studied therapy, a proportion of patients were censored upon a subsequent commencement of another DMT: 20 in the AHSCT group (mostly switching to anti-CD20 therapy or natalizumab), 20 in the cladribine group (mostly switching to sphingosine-1-phosphate modulators), and 102 in the alemtuzumab group (mostly switching to anti-CD20 therapies).

Effectiveness

The numbers of patients retained in the two pairwise matched comparisons are shown in Table 1. The matching procedure significantly decreased the differences in propensity scores between the compared groups from 0.32 to 0.014 for cladribine and from 0.33 to 0.007 for alemtuzumab vs. AHSCT, corresponding to 96% and 98% improvements in the overall balance, respectively. The close match on individual characteristics is demonstrated in Table 1 (standardised differences ≤10% for most of the matched characteristics and 13% for top prior therapy for the comparison against alemtuzumab). 27% of the AHSCT-treated patients and 38% of the DMT-treated patients were contributed by centres that included patients in both groups. The groups differed in between-visit intervals, for which the analyses were adjusted.

The 134 patients treated with AHSCT experienced fewer relapses than the 562 matched patients treated with cladribine (Figure 2; ARR, mean±standard deviation [SD] 0.05±0.28 vs. 0.15±0.39, respectively, $p<0.0001$). The number of patient-years needed to treat to prevent one relapse was 10. This observation was robust to unmeasured confounding ($\Gamma>2$) and was confirmed by the analysis of freedom from relapses (hazard ratio [HR]=0.24, 95% confidence interval [95%CI]=0.15-0.41). Most 6-month confirmed disability worsening events involved increase in

EDSS by 1 step (range 0.5 to 4.5). Annualised numbers of confirmed disability worsening events were 0.026 in the AHSCT group (where 5.2% experienced an event) and 0.040 in the cladribine group (where 7.1% experienced an event). We did not find evidence for difference in the cumulative hazard of the disability worsening over up to 3 years (HR=0.70, 95%CI=0.34-1.43). Most 6-month confirmed disability improvement events involved reduction in EDSS by 1 step (range 0.5 to 5). Annualised numbers of confirmed disability improvement events were 0.110 in the AHSCT group (where 11.4% experienced an event) and 0.054 in the cladribine group (where 7.3% experienced an event). AHSCT was superior to cladribine at facilitating the first 6-month confirmed improvement of disability (HR=2.19; 95%CI=1.31-3.66), corresponding to number needed to treat of 18 patient-years. These differences in disability outcomes were reflected by the tendency towards lower EDSS scores in the AHSCT group over time (Figure 2E, inset).

The ARR in the AHSCT group (143) was lower than in the matched alemtuzumab group (283; Figure 3; 0.04±0.23 vs. 0.09±0.21, respectively, p=0.02), as also confirmed by the analysis of freedom from relapses (HR=0.52, 95%CI=0.29-0.93). The number needed to treat to prevent one relapse was 20 patient-years. This observation was sensitive to potential unmeasured confounding (Γ=1.0). Annualised numbers of 6-month confirmed disability worsening events were 0.035 in the AHSCT group (where 10.2% experienced an event) and 0.037 in the alemtuzumab group (where 7.8% experienced an event). The study did not find evidence for difference in the first 6-month confirmed disability worsening between AHSCT and alemtuzumab over up to 5 years (HR=0.95, 95%CI=0.53-1.72). Annualised numbers of 6-month confirmed disability improvement events were 0.085 in the AHSCT group (where 16.3% experienced an event) and 0.045 in the alemtuzumab group (where 10.6% experienced an event). AHSCT was superior at facilitating the first 6-month confirmed disability improvement (HR=2.03; 95%CI=1.23-3.34), corresponding to number needed to treat of 25 patient-years. These differences in disability outcomes did not seem to translate into overall differential absolute EDSS scores over time (Figure 3E, inset).

The sensitivity analysis of patients who commenced their studied therapy after 2010 confirmed the findings of the primary analysis in full (Table 3).

The emulated trials were sufficiently powered to detect minimum differences in the hazard ratios for disability worsening of 20% for cladribine and 57% for alemtuzumab (eTable 7).

Safety

Safety data were available for the patients treated with AHSCT. Among the 163 patients who were matched in at least one of the pairwise analyses, 31 patients experienced febrile neutropenia during mobilisation, 16 patients experienced serum sickness, and 11 patients required ICU admission. 79 treatment-related adverse events were recorded in 56 patients after discharge post-AHSCT. These consisted mainly of infections (50; Table 2). No treatment-related deaths were reported among the matched AHSCT patients.

Discussion

This study of data from 7 AHSCT MS centres and the international MSBase registry emulated two trials comparing AHSCT with two immune-reconstitution disease modifying therapies in the treatment of highly active relapsing-remitting MS. The results showed that the ability of AHSCT to prevent relapses is considerably superior to both cladribine and alemtuzumab. The study did not find evidence for a difference in the probability of disability worsening between AHSCT and the comparator DMTs over up to 3-5 years but showed that AHSCT is associated with a higher rate of recovery from disability, especially during the initial year post-treatment.

To date, one phase 2 and one phase 3 (MIST) randomised controlled trial have compared AHSCT to conventional DMTs or broad immune-suppressing therapies in relapsing-remitting MS. These trials showed superiority of AHSCT in preventing localised, episodic inflammation (presenting as new or active cerebral T2 lesions or relapses) and confirmed worsening of disability.[13,29] The trials, however, used composite comparator arms, including approved and off-label interventions, ranging from interferon β to natalizumab or mitoxantrone, with or without add-on methylprednisolone, rituximab, plasmapheresis, cyclophosphamide or intravenous immunoglobulins. Results of a registry-based international study, which used more strictly defined comparator arms, demonstrated superiority of AHSCT in comparison to highly effective DMTs at reducing relapses and, similar to the MIST trial, facilitating early reduction of disability.[9] However, immune-reconstitution therapies were not included in any of these studies. Emerging data from the individual specialised transplant centres suggest that patients treated with AHSCT are potentially less likely to experience clinical or radiological disease activity than those

treated with alemtuzumab.[30-33] One study of propensity score overlap-weighted 103 patients treated with AHSCT followed up for to 5 years at a single centre showed that AHSCT was associated with a lower risk of relapses, similar risk of confirmed disability worsening and a higher probability of disability improvement in comparison to alemtuzumab.[34] The question whether the clinical effect of AHSCT in MS is synonymous with immune reconstitution or it represents more complex changes following profound immunodepletion remains to be answered.

Our present study compares the effectiveness of AHSCT with two potent immune-reconstitution DMTs in a typical clinical scenario in which AHSCT is used – in highly inflammatory relapsing MS among predominantly young patients who had accumulated moderate disability while treated mainly with high-efficacy DMTs. Interestingly, the superior effect of AHSCT on suppressing relapses does not immediately translate into reduced risk of further disability worsening when compared with cladribine and alemtuzumab within the 3-5-year observation period. However, it leads into more common partial recovery from the previously accumulated neurological disability. This is similar to the comparison of its effectiveness against two immune antitrafficking agents fingolimod and natalizumab. This phenomenon could be attributed to the immediate and broad elimination of lymphoid and myeloid cells that may enable prompt resolution of neuroinflammation and recovery of the reversibly disrupted function of the central nervous system.[1]

Cladribine induces >50% reduction in the circulating lymphocyte counts, including reduction of CD38+ memory B cells and attenuation of T-cell response to autoantigens.[35] Alemtuzumab reduces the CD4+ and CD8+ T and CD19+ B cells initially by >80%, however, it is followed by a rapid repopulation of B cells, which may lead to return of disease activity, and incomplete renewal of the T-call repertoire, which may contribute to secondary autoimmunity.[36] Further to temporarily eliminating all circulating immune cells, AHSCT reduces the number of dominant CD4+ and CD8+ T cell clones by >80%, with sustained reduction in the diversity of thymically-derived naïve CD4+ T cell repertoire.[37] Interestingly, the long-term changes to the immune system induced by AHSCT and alemtuzumab show many similarities. For example, in both therapies, B-cell population shifts from a predominantly transitional to a naïve phenotype and memory subpopulations remain suppressed over the long-term.[38-40]

The safety profile of AHSCT reported in this study is consistent with the previous experience. A considerable number of patients experienced febrile neutropenia during mobilisation with

cyclophosphamide, mostly related to doses exceeding 2g/m^2, and 7% required ICU admission. Almost one third of patients developed infectious complications following recovery from the transplant procedures. No AHSCT-related secondary autoimmunity, malignancy or death were reported among the matched patients over the man 3.9-year follow-up.

The main limitation of this study is its lack of true randomisation. We recognise that randomisation and blinding of trials comparing AHSCT to conventional therapies pose a considerable challenge.[41] We have therefore designed this study with the aim of emulating target trials using a large composite dataset from patients treated with AHSCT or DMTs and a well-established statistical methodology, thus mitigating treatment indication bias and attrition bias.[9] This approach also provides us with improved power and generalisability in comparison to smaller, single-site trials.[14] As the result of strict inclusion and matching criteria, we achieved a close alignment of the compared treatment groups on their demographic and clinical characteristics. While the comparison of AHSCT with cladribine was robust to unmeasured confounding, the comparison with alemtuzumab was vulnerable to potential unidentified confounders. Relapses represented one of the key outcomes of this study. Because identification of relapses followed a clinical definition and did not require independent adjudication or MRI-confirmation, heterogeneity of reporting may exist across the study sites. Matching on pre-baseline relapses and study region was used to mitigate this heterogeneity. We were unable to compare the safety for AHSCT and the DMTs but we have evaluated the systematically recorded safety information from the AHSCT cohort. While the safety protocols differed across the AHSCT sites, the key features were similar – including laboratory confirmation of the symptoms of treatment-related adverse events. The duration of the analysed follow-up, limited to the maximum of 3-5 years, restricted our ability to identify delayed effect of the suppression of inflammation on reduced accrual of disability. Because MRI information was unavailable in more than half of the study cohort, we did not include MRI in matching or as one of its outcomes. However, the MRI characteristics at baseline were similar between the matched groups where the information was available. Further, the available MRI information was only crude, and did not allow detailed evaluation of the extent and topography of the observed lesions. Our previous studies, however, did not show any effect of inclusion of MRI in matching on their results.[42,43] Different follow-up protocols may be used at different centres. We have therefore adjusted the models of disability outcomes for the frequency of visits with EDSS information. To account for

geographic differences in cohorts and outcomes,[44] we have matched patients on their geographic location. Some of the patients in the AHSCT group would be followed as part of open-label clinical trials. To mitigate this potential source of ascertainment bias, we have accounted for differences in follow-up by adjusting the outcomes models for the frequency of visits with EDSS scores. Adjustment of the analyses for conditioning regimens was presently not possible, as the regimens are often synonymous with AHSCT sites, and not represented in the DMT groups. To explore the effectiveness of different conditioning regimens, a dedicated study will be required. Similarly, to directly compare biological effects of the studied therapies, a prospective study design with harmonised acquisition of biological samples would be required.

Presently, four phase 3 randomised clinical comparative trials of AHSCT in relapsing-remitting MS are underway.[7] The RAM-MS (Scandinavia, Netherlands) and the STAR-MS (UK) trials will compare the efficacy of AHSCT (using cyclophosphamide + anti-thymocyte globulin conditioning) against alemtuzumab, cladribine, ocrelizumab and ofatumumab (STAR-MS only). The BEAT-MS (USA) and the NET-MS (Italy) trials will compare the efficacy of AHSCT (using BEAM + anti-thymocyte globulin conditioning) against alemtuzumab, cladribine, natalizumab, and a broad spectrum of anti-CD20 therapies. Subgroup analyses of these trials will probably enable comparisons of the efficacy of AHSCT with cladribine and alemtuzumab, depending on the available power to perform such analyses. The results of these trials are expected to become available over the next quinquennium.

Conclusion

In this study, we show that over 3-5 years, the effect of AHSCT on suppressing relapses and facilitating recovery from disability in highly active relapsing-remitting MS exceeds conventional immune-reconstitution therapies cladribine and alemtuzumab. AHSCT is associated with considerable risks, especially of infectious complications, but this study did not report any treatment-related mortality. Among patients with highly inflammatory MS phenotype, especially with suboptimal response to conventional DMTs,[45] the broad and complete immune suppression combined with reconstitution of immune repertoire induced by AHSCT poses an attractive therapeutic pathway. Comparison of the durability of AHSCT and immune reconstitution DMTs will deserve further research, once data from cohorts with long-term follow-up become available.

Data availability

Data from the participating cohorts can be requested from the principal investigators, conditional after obtaining approvals from the appropriate institutional review boards. The MSBase registry is a data processor and warehouses data from individual principal investigators who agree to share their datasets on a project-by-project basis. Data access to external parties can be granted on reasonable request at the sole discretion of the principal investigators, who will need to be approached individually for permission.

Acknowledgements

Tomas Kalincik and Sifat Sharmin had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The MSBase Foundation is a not-for-profit organization that receives support from Merck, Biogen, Novartis, Bayer-Schering, Sanofi-Genzyme and Teva. The study was conducted separately and apart from the guidance of the sponsors. We thank the MSBase Operations team Charlotte Sartori, Eloise Hinson, Pamela Farr, Rein Moore, Dusko Stupar, Cynthia Tang and Sonya Smirnova.

Funding

This study was financially supported by National Health and Medical Research Council of Australia [fellowship 2026836, project grant 1129189] and Multiple Sclerosis Australia [projects 19-800 and 22-2-103]. Part of the data acquisition was funded by the MS Foundation of Canada. All aspects of the study were completed independent and separate from the funders.

Competing interests

Tomas Kalincik served on scientific advisory boards for MS International Federation and World Health Organisation, BMS, Roche, Janssen, Sanofi Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by Sanofi Genzyme, received conference travel

support and/or speaker honoraria from WebMD Global, Eisai, Novartis, Biogen, Roche, Sanofi-Genzyme, Teva, BioCSL and Merck and received research or educational event support from Biogen, Novartis, Genzyme, Roche, Celgene and Merck. **Izanne Roos** served on scientific advisory boards/steering committees for Novartis and Merck and received conference travel support and/or speaker honoraria from Roche, Novartis, Biogen, Teva, Sanofi-Genzyme and Merck. **Jennifer Massey** served on scientific advisory board for Roche, received conference travel support and/or speaker honoraria from Novartis, Biogen, Roche and Merck. **Ian Sutton** received compensation for an educational activity from Biogen. **Oivind Torkildsen** received speaker honoraria from and served on scientific advisory boards for Biogen, Sanofi-Aventis, Merck and Novartis. **Lars Bø** received speaker honoraria from Novartis, and consultant fees from Viatris. **Eva Kubala Havrdova** received honoraria/research support from Biogen, Merck Serono, Novars, Roche, and Teva; has been member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novars, and Sanofi Genzyme; received honoraria/research support from Biogen, Merck Serono, Novars, Roche, and Teva; has been member of advisory boards for Actelion, Biogen, Celgene, Merck Serono, Novars, and Sanofi Genzyme; and has been supported by the Czech Ministry of Education – project Cooperatio LF1, research area Neuroscience, and the project National Institute for Neurological Research (Programme EXCELES, ID project No LX22NPO5107) – funded by the European Union-Next Generation EU. **Marek Trneny** received honoraria from Janssen, Gilead Sciences, Bristol-Myers Squibb, Takeda, Amgen, Abbvie, Roche, MorphoSys, Novartis, served as an advisor to Takeda, Bristol-Myers Squibb, Incyte, Abbvie, Amgen, Roche, Gilead Sciences, Janssen, MorphoSys, Novartis, and received conference travel support from Gilead Sciences, Takeda, Bristol-Myers Squibb, Roche, Janssen and Abbvie. **Richard Macdonell** received compensation for traveling, conference fees and consulting fees from Merck, Teva, Sanofi Genzyme, Biogen Idec, Novartis, Roche, BMS, Celgene. **Will Brown** reports speaking honoraria from The Corpus, Biogen and Novartis; and advisory board fees from Biogen and Intesso. **Anneke van der Walt** served on advisory boards and receives unrestricted research grants from Novartis, Biogen, Merck and Roche She has received speaker's honoraria and travel support from Novartis, Roche, and Merck. She receives grant support from the National Health and Medical Research Council of Australia and MS Research Australia. **Helmut Butzkueven** received institutional (Monash University) funding from Biogen, Roche, Merck, Alexion and Novartis; has carried out contracted research for Novartis, Merck, Roche and Biogen; has taken part in speakers' bureaus for Biogen, Novartis, Roche and Merck; has received

personal compensation from Oxford Health Policy Forum for the Brain Health Steering Committee. **Bart Van Wijmeersch** has received speaker fees, research support and travel grants from Almirall, Actelion/Janssen, Bayer, Biogen, Celgene/BMS, Imcyse, Merck, Novartis, Roche, Sanofi Genzyme and Teva. **Jeannette Lechner-Scott** travel compensation from Novartis, Biogen, Roche and Merck. Her institution receives the honoraria for talks and advisory board commitment as well as research grants from Biogen, Merck, Roche and Novartis. **Michael Barnett** received compensation for speaking from Biogen, Merck, Roche, Alexion and Novartis. His institution has received research support from Biogen, Roche, Merck, BMS, Alexion and Novartis. He is a co-founder of RxPx and Sydney Neuroimaging Analysis Centre. **Guy Laureys** received travel and/or consultancy compensation from Sanofi-Genzyme, Roche, Teva, Merck, Novartis, Celgene, Biogen. **Barbara Willekens** received honoraria for acting as a member of Scientific Advisory Boards/Consultancy for Alexion, Almirall, Biogen, Celgene/BMS, Merck, Janssen, Novartis, Roche, Sandoz, Sanofi-Genzyme and speaker honoraria and travel support from Biogen, Celgene/BMS, Merck, Novartis, Roche, Sanofi-Genzyme; research and/or patient support grants from Biogen, Janssen, Merck, Sanofi-Genzyme, Roche. Honoraria and grants were paid to UZA/UZA Foundation. Further, B.W. received research funding from FWO-TBM, Belgian Charcot Foundation, Start2Cure Foundation, Queen Elisabeth Medical Foundation for Neurosciences and the National MS Society USA. **Katherine Buzzard** received speaker honoraria and/or education support from Biogen, Teva, Novartis, Genzyme-Sanofi, Roche, Merck and Alexion; has been a member of advisory boards for Merck and Biogen. **Olga Skibina** received honoraria and consulting fees from Bayer Schering , Novartis, Merck, Biogen and Genzyme. **Suzanne Hodgkinson** has received consulting fees and speaker honoraria from Biogen, Novartis, Roche, Merck, and has received grants for her Institution from Biogen, Merck, Novartis, and Roche. **Jose E Meca-Lallana** has received grants and consulting or speaking fees from Alexion, Almirall, Biogen, Bristol-Meyers-Squibb, Horizon, Janssen, Merck, Novartis, Roche, Sandoz and Sanofi. **Raed Alroughani** received honoraria as a speaker and for serving on scientific advisory boards from Bayer, Biogen, GSK, Merck, Novartis, Roche and Sanofi-Genzyme. **Julie Prevost** accepted travel compensation from Novartis, Biogen, Genzyme, Teva, and speaking honoraria from Biogen, Novartis, Genzyme and Teva. **Matteo Foschi** received travel and meeting attendance support from Novartis, Biogen, Roche, Sanofi-Genzyme and Merck. **Andrea Surcinelli** received travel and meeting attendance support from Novartis, Biogen, Roche, Merck, Bristol, Sanofi-Genzyme, Almirall, Piam. **Sara Eichau** have received

speaker honoraria and consultant fees from Biogen Idec, Novartis, Merck, Janssen, Bristol-Meyers, Bayer, Sanofi Genzyme, Roche and Teva **Pamela McCombe** received speakers fees and travel grants from Novartis, Biogen, T'évalua, Sanofi. **Nevin John** is a PI on commercial MS studies sponsored by Novartis, Roche, Biogen and Sanofi. He has received speaker's honoraria from Merck. He has had conference travel and registration reimbursement from Novartis. **Simón Cárdenas-Robledo** has received in the past three years travel expenses for scientific meetings from Biopas, Roche, Merck, and Genzyme; compensation for consulting services or participation on advisory boards from Merck, Biogen-Idec, Sanofi and Novartis; lecture fees from Novartis, Merck, Sanofi, Janssen and Biogen-Idec; and research support from Biogen-Idec and Novartis. He is a subject editor on Multiple Sclerosis for Acta Neurológica Colombiana and a member of the editorial board of Frontiers of Neurology. **Jiwon Oh** has received research funding from the MS Society of Canada, National MS Society, Brain Canada, Biogen, Roche, EMD Serono (an affiliate of Merck KGaA); and personal compensation for consulting or speaking from Alexion, Biogen, Celgene (BMS), EMD Serono (an affiliate of Merck KGaA), Novartis, Roche, and Sanofi-Genzyme. **Jose Luis Sanchez-Menoyo** accepted trave compensation from Novartis, Merck and Biogen, speaking honoraria from Biogen, Novartis, Sanofi, Merck, Almirall, Bayer and Teva and has participated in clinical trials by Biogen, Merck and Roche. **Francesco Patti** received personal compensation for serving on advisory board by Almirall, Alexion, Biogen, Bristol, Janssen, Merck, Novartis and Roche. He further received research grant by Alexion, Almirall, Biogen, Bristol, Merck, Novartis and Roche and by FISM, Reload Association (Onlus), Italian Health Minister, and University of Catania. **Yolanda Blanco** received speaker honoraira/consulting fees from Merck, Biogen, Roche, Brystol, Novartis, Sanofi and Sandoz. **Pierre Grammond** has served in advisory boards for Novartis, EMD Serono, Roche, Biogen idec, Sanofi Genzyme, Pendopharm and has received grant support from Genzyme and Roche, has received research grants for his institution from Biogen idec, Sanofi Genzyme, EMD Serono. **John Snowden** declares honoraria for educational events from Jazz, Gilead, Janssen, for advisory board membership from Medac, and for trial IDMC membership from Kiadis Pharma. **Sifat Sharmin, Mark S. Freedman, Harold Atkins, Barbara Withers, Joachim Burman, Anne Kristine Lehmann, Eva Krasulova, Tomas Kozak, Alisdair Coles, Serkan Ozakbas, Basil Sharrack, Oliver Gerlach, Stefano Neri** have nothing to disclose.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 Consort diagram of patient disposition. AHSCT, autologous hematopoietic stem cell transplantation; MS, multiple sclerosis.

Figure 2 Comparative effectiveness of AHSCT and cladribine. AHSCT, autologous hematopoietic stem cell transplantation; 95%CI, 95% confidence interval.

Figure 3 Comparative effectiveness of AHSCT and alemtuzumab. AHSCT, autologous hematopoietic stem cell transplantation; 95%CI, 95% confidence interval.

Table 1 Characteristics of the matched patient groups at baseline

	AHSCT	Cladribine	d	AHSCT	Alemtuzumab	d
Patients matched	134	562		143	283	
Sex, M (%)	40 (29.9)	170 (30.3)	0.01	42 (29.4)	81 (28.7)	0.02
Age (mean (SD))	36.8 (8.7)	37.0 (10.3)	0.02	35.8 (9.1)	36.3 (8.5)	0.07
MS duration, y (mean (SD))	8.34 (5.35)	8.40 (6.18)	0.01	8.19 (5.83)	8.61 (5.72)	0.07
Relapses in prior 12 months (mean (SD))	0.60 (0.93)	0.61 (0.76)	0.00	0.60 (0.90)	0.59 (0.82)	0.02
Relapses in prior 24 months (mean (SD))	0.84 (1.22)	0.83 (0.99)	0.01	0.87 (1.20)	0.84 (1.04)	0.03
Baseline disability, EDSS (median (quartiles))	3.5 (2.5, 4.5)	3.5 (2.0, 6.0)	0.03	3.5 (2.4, 5.0)	3.5 (2.0, 5.0)	0.05
Patients with progression within 1 year pre-baseline (%)	24 (17.9)	101 (18.0)	0.00	23 (16.1)	39 (13.9)	0.06
Most effective pre-baseline DMT (%)			0.04			0.13
Low-efficacy	27 (20.1)	111 (19.9)		22 (15.4)	46 (16.4)	
Medium-efficacy	29 (21.6)	127 (22.6)		30 (21.0)	63 (22.4)	
High-efficacy	56 (41.8)	237 (42.3)		67 (46.9)	139 (49.2)	
Unknown	22 (16.4)	85 (15.2)		24 (16.8)	34 (12.1)	
Region (%)			0.06			0.10
Asia-Pacific	48 (35.8)	210 (37.4)		49 (34.3)	107 (37.8)	
Europe	63 (47.0)	249 (44.3)		74 (51.7)	132 (46.6)	
North America	23 (17.2)	103 (18.4)		20 (14.0)	44 (15.5)	
Study follow-up, y (mean (SD))	3.91 (2.57)	1.93 (0.94)	1.02	3.80 (2.53)	4.40 (1.66)	0.28
Year of baseline (median [IQR])	2016 [2014, 2017]	2019 [2019, 2020]	1.22	2016 [2014, 2017]	2016 [2015, 2017]	0.22
MRI within 1 year pre-baseline: T2 lesion number (%)			0.44			0.32
0	0 (0.0)	1 (0.1)		0 (0.0)	0 (0.0)	
1–2	1 (0.7)	7 (1.3)		1 (0.7)	1 (0.3)	
3-8	1 (0.7)	38 (6.7)		3 (2.1)	17 (5.9)	
9+	46 (34.3)	253 (44.9)		45 (31.5)	119 (41.9)	
Unknown	86 (64.2)	264 (47.0)		94 (65.7)	147 (51.9)	
Post-baseline visit interval, months (mean (SD))	8.09 (3.79)	5.87 (4.21)	0.56	7.87 (3.59)	7.46 (4.86)	0.10

The patient characteristics are presented for each pair of matched treatment groups separately. Low-efficacy therapies: interferons β, glatiramer acetate, teriflunomide; medium-efficacy therapies: dimethyl fumarate, fingolimod, daclizumab, cladribine; high-efficacy therapies: natalizumab, alemtuzumab, ocrelizumab, rituximab, mitoxantrone. AHSCT, autologous haematopoietic stem cell transplant; d, standardised difference (Cohen's d); SD, standard deviation; EDSS, Expanded Disability Status Scale; IQR, interquartile range

Table 2 Treatment-related adverse events reported after AHSCT

Adverse event	Number of events
Infections	
Epstein-Barr virus	11
Cytomegalovirus	10
Herpes simplex or zoster	8
Influenza	2
Other viral	2
Bacterial	7
Upper respiratory tract infection	3
Lower respiratory tract infection	2
Urinary tract infection	3
Sepsis	2
Haematological	
Thrombosis	3
Thrombocytopenia	1
Gastrointestinal	
Colitis	2
Mallory-Weiss syndrome	1
Endocrinological	
Hypothyroidism	2
Ovarian failure	1
Adrenal insufficiency	1
Fever of unknown aetiology	2
Acute kidney injury	1
Lymphadenopathy	1
Arthralgia	1
Other	9

Table 3 Sensitivity analysis of patients treated after year 2010

	AHSCT versus cladribine	AHSCT versus alemtuzumab
Patients, n	117 versus 555	128 versus 259
Annualised relapse rate, ± standard deviation	0.04 ± 0.26 versus 0.14 ± 0.35 (p < 0.0001)	0.03 ± 0.21 versus 0.11 ± 0.23 (p < 0.0001)
Relapse, HR (95%CI)	0.22 (0.11–0.44)	0.27 (0.13–0.59)
Confirmed disability worsening, HR (95%CI)	1.10 (0.51–2.39)	1.51 (0.61–3.74)
Confirmed disability improvement, HR (95%CI)	2.32 (1.38–3.91)	2.10 (1.17–3.78)

95%CI, 95% confidence interval HR, hazard ratio.

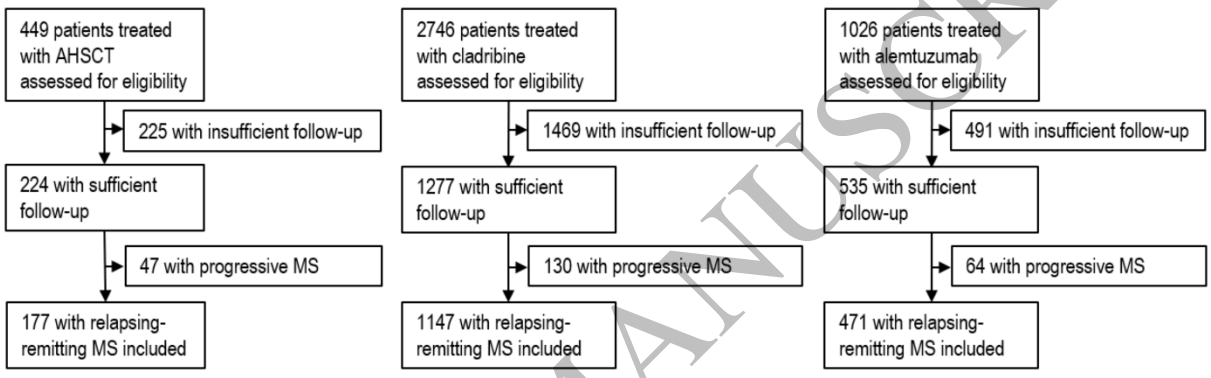

Figure 1
160x49 mm (x DPI)

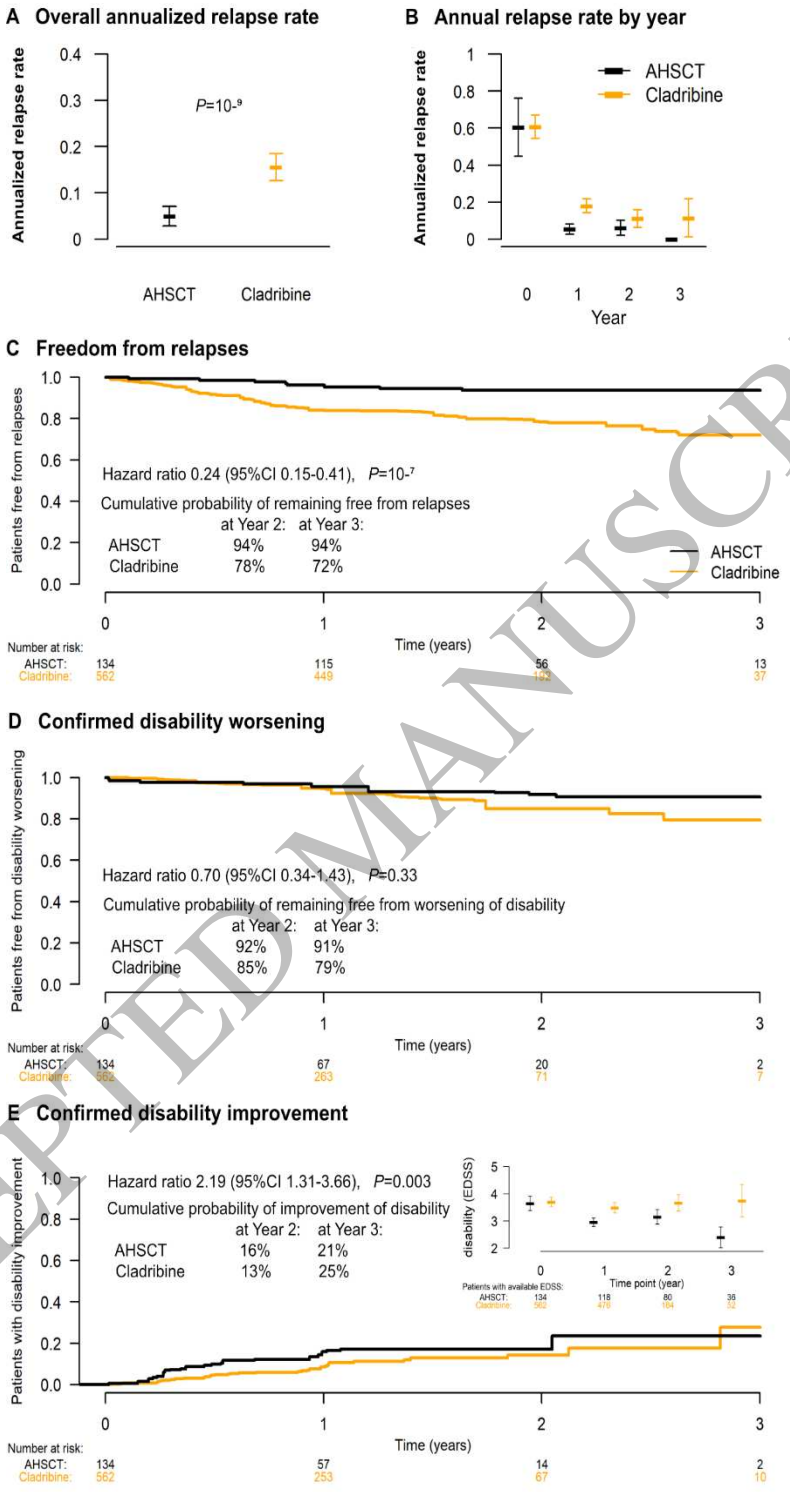

Figure 2
149x252 mm (x DPI)

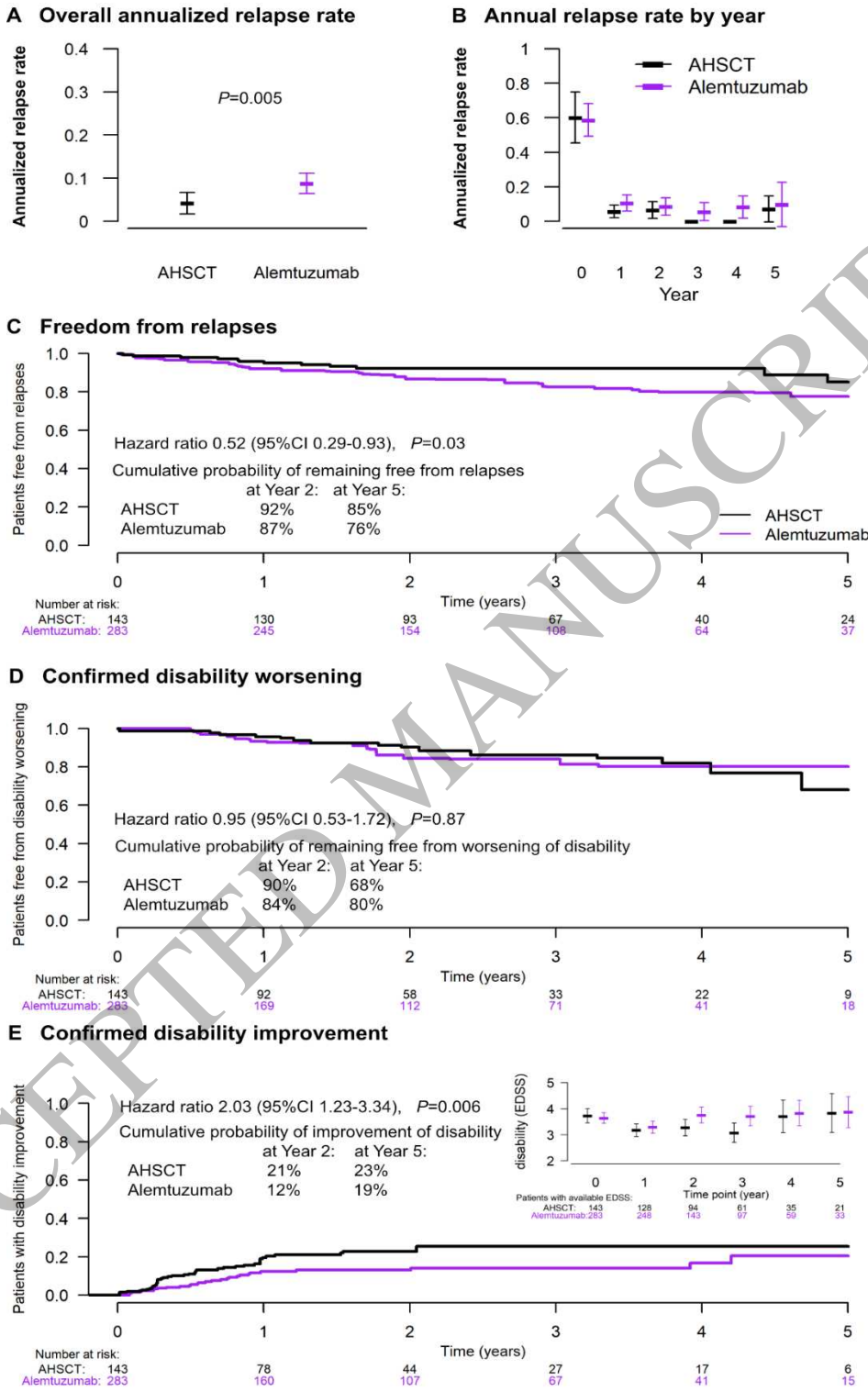

Figure 3
147x252 mm (x DPI)

TYSABRI™ (natalizumab)
SUBCUTANEOUS USE | 300mg

Prescribing Information

Efficacy made Convenient

TYSABRI SC injection with the potential to administer **AT HOME** for eligible patients*

Efficacy and safety profile comparable between TYSABRI IV and SC†[1,2]

†Comparable PK, PD, efficacy, and safety profile of SC to IV except for injection site pain.[1,2]

CLICK HERE TO DISCOVER MORE ABOUT TYSABRI SC AND THE DIFFERENCE IT MAY MAKE TO YOUR ELIGIBLE PATIENTS

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A Biogen developed and funded JCV antibody index PML risk stratification service, validated and available exclusively for patients on or considering TYSABRI.

*As of April 2024, TYSABRI SC can be administered outside a clinical setting (e.g. at home) by a HCP for patients who have tolerated at least 6 doses of TYSABRI well in a clinical setting. Please refer to section 4.2 of the SmPC.[1]

TYSABRI is indicated as single DMT in adults with highly active RRMS for the following patient groups:[1,2]

- **Patients with highly active disease despite a full and adequate course of treatment with at least one DMT**
- **Patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in one year, and with 1 or more Gd+ lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI**

Very common AEs include nasopharyngitis and urinary tract infection. Please refer to the SmPC for further safety information, including the risk of the uncommon but serious AE, PML.[1,2]

Abbreviations: AE: Adverse Event; **DMT:** Disease-Modifying Therapy; **Gd+:** Gadolinium-Enhancing; **HCP:** Healthcare Professional; **IV:** Intravenous; **JCV:** John Cunningham Virus; **MRI:** Magnetic Resonance Imaging; **PD:** Pharmacodynamic; **PK:** Pharmacokinetic; **PML:** Progressive Multifocal Leukoencephalopathy; **RRMS:** Relapsing-Remitting Multiple Sclerosis; **SC:** Subcutaneous.

References: 1. TYSABRI SC (natalizumab) Summary of Product Characteristics. **2.** TYSABRI IV (natalizumab) Summary of Product Characteristics.

Adverse events should be reported. For Ireland, reporting forms and information can be found at www.hpra.ie. For the UK, reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ or via the Yellow Card app available from the Apple App Store or Google Play Store. Adverse events should also be reported to Biogen Idec on MedInfoUKI@biogen.com 1800 812 719 in Ireland and 0800 008 7401 in the UK.

Biogen-261128. DOP: April 2025

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