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Title:
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Date:
2024

Citation:
Kalincik, T., Sharmin, S., Massey, J., Sutton, I., Withers, B., Freedman, M. S., Atkins, H., Krasulova, E., Havrdova, E. K., Trneny, M., Kozak, T., Burman, J., MacDonell, R., Torkildsen, Ø., Bø, L., Lehmann, A. K., Sharrack, B. & Snowden, J. (2024). Effectiveness of autologous haematopoietic stem cell transplantation versus natalizumab in progressive multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry, 95 (8), pp.775-783. https://doi.org/10.1136/jnnp-2023-332790.

Title :

Effectiveness of autologous haematopoietic stem cell transplantation versus natalizumab in progressive multiple sclerosis

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on behalf of the MS-RESCUE network and the MSBase Study Group[#]

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Word count, manuscript: 3104
Word count, abstract: 267
References: 39
Figures: 4
Tables: 2
The manuscript includes online supplementary material.
Statistical Analysis Plan, v.12, 9th July 2019:
https://osf.io/b3w6p/?view_only=cf31816e9cc14cb681cf0ed05e098a53

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

KEY MESSAGES

What is already known on this topic

No randomised clinical trials and only a limited number of non-randomised studies have explored whether autologous hematopoietic stem cell transplantation (AHSCT) is effective in improving disability outcomes in progressive multiple sclerosis (MS).

What this study adds

This observational study, utilising a composite cohort from specialised MS centres and the MSBase international registry, compares the effectiveness of AHSCT to natalizumab in patients with primary and secondary progressive multiple sclerosis. Natalizumab was not shown to be effective in controlling disability in non-active progressive multiple sclerosis, and therefore serves as an appropriate comparator to study superiority of AHSCT. This study shows that AHSCT is not superior to natalizumab in preventing disability worsening, allowing disability improvement and preventing relapses over 4 years.

How this study might affect research, practice or policy

AHSCT cannot be justified as a therapy among patients with progressive multiple sclerosis with low level of relapse activity.

ABSTRACT

Background: Natalizumab was not shown to modify disability in progressive multiple sclerosis (MS). This matched observational study compared the effectiveness of autologous hematopoietic stem cell transplantation (AHSCT) with natalizumab in progressive MS.

Methods: Patients with primary/secondary progressive MS from 7 AHSCT MS centres and the MSBase registry, treated with AHSCT or natalizumab were matched on a propensity score derived from sex, age, Expanded Disability Status Scale (EDSS), number of relapses 12/24 months before baseline, time from MS onset, the most effective prior therapy and country. The pairwise-censored groups were compared on hazards of 6-month confirmed EDSS worsening and improvement, relapses and annualised relapse rates (ARR), using Andersen-Gill proportional hazards models and conditional negative binomial model.

Findings: 39 patients treated with AHSCT (37 with secondary progressive MS, mean age 37 years, EDSS 5.7, 28% with recent disability progression, ARR 0.54 during the preceding year) were matched with 65 patients treated with natalizumab. The study found no evidence for difference in hazards of confirmed EDSS worsening (hazard ratio 1.49, 95% confidence interval [95%CI] 0.70-3.14) and improvement (hazard ratio 1.50, 95%CI 0.22-10.29) between AHSCT and natalizumab over up to 4 years. The relapse activity was also similar while treated with AHSCT and natalizumab (ARR: mean±standard deviation 0.08±0.28 vs. 0.08±0.25; hazard ratio 1.05, 95%CI 0.39-2.82). In the AHSCT group, 3 patients experienced febrile neutropenia during mobilisation, 9 patients experienced serum sickness, 6 patients required ICU admission, and 36 patients experienced complications after discharge. No treatment-related deaths were reported.

Conclusion: This study does not support the use of AHSCT to control disability in progressive MS with advanced disability and low relapse activity.

TEXT

INTRODUCTION

Autologous hematopoietic stem cell transplantation following chemotherapy (AHSCT) is a potent immunosuppressant therapy that has occasionally been used in progressive forms of multiple sclerosis (MS). It is effective in suppressing inflammation within the central nervous system through ablation and reconstitution of the immune system.[1] Its effectiveness has been demonstrated in highly active and refractory forms of relapsing-remitting MS.[2-4] In progressive MS, conflicting results were reported by two observational studies that compared the effectiveness of AHSCT on disability outcomes in secondary progressive disease to a mixed group of immunomodulatory therapies or pulsed cyclophosphamide, one of which included patients with high level of relapse activity.[5,6]

Significant treatment toxicity is common in AHSCT and most commonly includes infections and febrile neutropenia. Treatment-related mortality is reported to range from 0.3% to 2% and has been on decline, mainly thanks to improved transplant centre experience and patient selection.[1,7,8]

Given the risks associated with AHSCT, it is important to establish whether its profound and sustained effect observed in highly inflammatory relapsing-remitting MS is also seen in non-active progressive MS.[7] Only a limited number of disease modifying therapies have shown a positive effect in progressive MS.[9,10] Interestingly, natalizumab, a potent inhibitor of immune cell migration across the blood-brain barrier through α4β1-integrin - VCAM-1 interaction, was not reported to be effective at preventing disability in non-active secondary progressive MS.[11] It therefore represents an interesting comparator for a study that aims to establish evidence for or against the effect of AHSCT in progressive MS. In the absence of randomised controlled trials, studies of high-quality cohorts have helped establish the comparative effectiveness among DMTs as well as AHSCT in relapsing-remitting MS.[3,12-16] In scenarios where randomised trials would not be feasible, emulated clinical trials in observational data can support treatment decisions[17,18] In this study, we have examined the question whether AHSCT is effective in preventing or reversing disability in progressive MS with low-level relapse activity. We have

done this by emulating a trial that compares clinical effectiveness of AHSCT with natalizumab among patients with progressive MS.

METHODS

Patients and data

Data, recorded between 1999-2021, were obtained from patients treated with AHSCT at 7 specialised centres (in Ottawa, Sheffield, Prague, Uppsala, Bergen, Sydney and Melbourne) participating in the MS-RESCUE network and 39 centres in 11 countries from the MSBase registry. The study was approved by the Melbourne Health Human Research Ethics Committee [2006.044] and the site institutional review boards and is registered with WHO (ACTRN12605000455662). Patients provided written informed consent, as required.

The inclusion criteria were primary progressive MS (as per McDonald 2005, 2010 or 2017 diagnostic criteria)[19-21] or secondary progressive MS (as per the Lublin definition)[22] as diagnosed by treating neurologists, first exposure to AHSCT or natalizumab, minimum recorded follow-up of 2 months prior to treatment start and ≥2 post-baseline disability scores (including ≥1 on treatment), minimum persistence on natalizumab of 3 months and minimum dataset (consisting of sex, age, date of first MS symptom, dates of clinical relapses, clinical MS course, disability score at treatment commencement (-9 months to +1 month)). All eligible patients treated with AHSCT at the study centres between August 1999 and July 2020 were enrolled consecutively.

Procedures

Patients received AHSCT following protocols specific to the treating centres.[23-26] Autologous haematopoietic stem cells were mobilised using cyclophosphamide 2-4.5 g/m^2 IV with granulocyte colony stimulating factor 5-10μg/kg. The cells were then harvested by leukapheresis and cryopreserved. In almost a half 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/m², etoposide 200-800mg/m², cytarabine 200mg/m² and melphalan 140mg/m²), busulfan with cyclophosphamide 50mg/kg, or cyclophosphamide 200mg with anti-thymocyte globulin 10mg/kg. Rabbit/horse anti-thymocyte globulin was used in 87% of patients. Infection prophylaxis was used as per local protocols. The patients included in the comparator group were treated with natalizumab (300mg IV every 4 weeks).

Baseline was defined as the first day of AHSCT conditioning or first dose of natalizumab. Patients were censored at discontinuing therapy (with the minimum duration of treatment effect set at 5 years after AHSCT and 60 days after starting natalizumab),[27] commencing another DMT, or at the last recorded disability score, whichever occurred first.

The analysed data were recorded as part of routine practice at tertiary MS services, with real-time data entry. The study protocol stipulates minimum annual acquisition of disability scores, but patients with less frequent visits were not excluded.[28] Data from different sources were mapped, combined and underwent a rigorous quality procedure (Supplementary Table 2).[29]

Outcomes

The primary endpoint was the cumulative hazard of disability worsening. Secondary endpoints were the cumulative hazards of disability improvement, the on-treatment annualised relapse rate (ARR) and the cumulative hazard of relapses.

Disability was scored by Expanded Disability Status Scale (EDSS) raters (with Neurostatus certification at each site), excluding scores recorded ≤30 days of a prior relapse. Disability worsening was defined as an increase in EDSS by 1 step (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 (1.5 step if baseline EDSS=1.5 and 0.5 steps if baseline EDSS>6) confirmed by subsequent EDSS scores over ≥6 months.[30]

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.[31] Confirmation of relapses by EDSS was not mandated. Individual ARR between baseline and censoring was calculated.

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. Only partial safety information was available in the natalizumab group, including progressive multifocal leukoencephalitis and mortality.

Statistical analysis

This study emulated a clinical trial comparing AHSCT with natalizumab using the protocol by Hernan and Robins (Supplementary Table 3).[32] Matching and statistical analyses were conducted using R (v4.1.1).[33] Individual patients were matched on their propensity of receiving AHSCT vs. natalizumab in optimal 1:3 variable matching ratio without replacement within a caliper of 0.2 standard deviations of the propensity score. Individual propensity scores were calculated using a multivariable logistic regression of treatment allocation that used patient characteristics 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. The pairwise censoring of on-treatment follow-up was used to mitigate attrition bias, informative censoring and the effect of differences in the definition of treatment persistence.[13] The time at censoring was determined in each matched pair as the shorter of the follow-up times of the two participants.

The cumulative hazards of disability worsening events, disability improvement events and relapses were evaluated with weighted conditional proportional hazards models of multiple events (Andersen-Gill) with robust estimation of variance, adjusted for age, time from MS onset

and year at baseline (to mitigate residual imbalance), and visit frequency. Schoenfeld's global test was used to examine the proportionality of hazards. ARRs were compared with a weighted negative binomial model with cluster effect for matched pairs.

Robustness of the statistically significant differences to unidentified confounders was quantified with Hodges-Lehmann Γ.[34] Where no evidence of difference between the compared groups was found, the minimum detectable effect at α=0.05 and 1-β=0.80 was estimated with 200 simulations per treatment pair and outcome.

RESULTS

The study identified 39 eligible patients treated with AHSCT and 119 patients treated with natalizumab (Figure 1). As expected, the unmatched groups differed in their baseline characteristics (Supplementary Table 4). From the multivariable logistic regression model used to derive the propensity scores, it can be seen that the included patients were more likely to commence AHSCT at a younger age, earlier from MS onset, and when resident in the Asia-Pacific region, and less likely after being previously treated only with medium-efficacy disease modifying therapies, when compared to natalizumab (Supplementary Table 5).

The numbers of patients retained in matched comparison were 39 in the AHSCT group and 65 in the natalizumab group (Table 1). The matching significantly decreased the mean difference in the propensity score between the compared groups from 0.52 to 0.025, corresponding to a 95% relative improvement in the overall balance. This improvement is depicted in Figure 2 and the resulting match on individual characteristics is shown in Table 1. While for most patient characteristics, the achieved balance was satisfactory (Cohen's d≤0.2 pooled standard deviation), for age, time from MS onset and year at baseline considerable residual imbalance persisted. Further, the patients were not matched on the frequency of specialist clinic visits. The analyses were therefore adjusted for these characteristics. As a result of pairwise censoring, on-treatment follow-up was identical in the matched groups.

Table 1

Characteristics of the matched patient groups at baseline

	AHSCT	natalizumab	d
patients matched	39	65	
sex, M (%)	14 (35.9)	20 (30.8)	0.11
age (mean (SD))	36.8 (8.6)	43.9 (9.2)	0.80
MS duration, y (mean (SD))	10.4 (6.7)	13.8 (6.7)	0.51
MS phenotype (%)			
secondary progressive	37 (94.9)	53 (81.5)	
primary progressive	2 (5.2)	12 (18.4)	
relapses in prior 12 months (mean (SD))	0.54 (0.82)	0.61 (0.94)	0.08
patients with relapses in prior 12 months (%)	15 (38.4)	29 (44.6)	
relapses in prior 24 months (mean (SD))	0.90 (1.25)	0.94 (1.17)	0.04
patients with relapses in prior 24 months (%)	20 (51.3)	36 (55.4)	
baseline EDSS (mean (SD))	5.7 (1.2)	5.7 (1.4)	0.02
patients with pre-baseline progression (%)	11 (28.2)	13 (19.7)	0.20
top pre-baseline DMT (%)			0.12
low-efficacy	10 (25.6)	15 (23.1)	
medium-efficacy	1 (2.6)	2 (2.6)	
high-efficacy	3 (7.7)	7 (10.3)	
unknown	25 (64.1)	41 (64.1)	
region (%)			0.30
Asia-Pacific	18 (46.2)	29 (45.3)	
Europe	10 (25.6)	24 (36.8)	
North America	11 (28.2)	12 (17.9)	
post-baseline follow-up, y (mean (SD))	6.24 (3.11)	2.69 (2.39)	1.28
year of baseline (median [IQR])	2013 [2004, 2015]	2011 [2008, 2013]	0.13
brain MRI: T2 lesion number (%)			0.78
0	0 (0.0)	2 (2.6)	
1-2	0 (0.0)	13 (20.5)	
3+	24 (61.5)	29 (45.3)	
unknown	15.0 (38.5)	21 (31.6)	
visits per year (mean (SD))	1.00 (0.00)	1.30 (0.53)	0.79

low-efficacy therapies: interferons β, glatiramer acetate, teriflunomide;
medium-efficacy therapies: dimethyl fumarate, fingolimod, cladribine;
high-efficacy therapies: natalizumab, alemtuzumab, ocrelizumab, rituximab. mitoxantrone;
d, standardised difference (Cohen's d); SD, standard deviation; EDSS, Expanded Disability Status Scale;
IQR, interquartile range

The comparison of treatment effectiveness found no evidence for difference between AHSCT and natalizumab when used in progressive MS. The cumulative hazard of 6-month confirmed disability worsening was similar in the two groups (hazard ratio [HR]=1.49, 95% confidence interval [95%CI]=0.70-3.14) over up to 4 years, with median matched follow-up of 1.98 years (quartiles 1.26, 3.00; Figure 3). Similarly, no evidence of difference was found for the cumulative probability of 6-month confirmed disability improvement (HR=1.50; 95%CI=0.22-10.28).

Patients with progressive MS treated with AHSCT experienced a similar number of relapses as those treated with natalizumab (Figure 4; mean±standard deviation 0.08±0.28 vs. 0.08±0.25, respectively). This observation was corroborated by the cumulative hazard of relapses (HR=1.05, 95%CI 0.39-2.82).

According to the power analysis, this emulation of a trial was sufficiently powered to detect minimum differences of 75% in cumulative hazard of disability worsening events, 89% in cumulative hazard of disability improvement events, 0.17 relapses per year and 62% difference in cumulative hazard of relapses between the compared therapies.

Complete safety data were available for the patients treated with AHSCT. Most patients experienced an adverse event associated with AHSCT (36/39 patients). Three patients experienced febrile neutropenia during mobilisation, 9 patients experienced serum sickness, and 6 patients required ICU admission. Thirty-four adverse events potentially associated with AHSCT were recorded after the completion of treatment and post-discharge (Table 2). These included 24 infectious complications, most commonly reactivation of herpes zoster and cytomegalovirus. None of the patients treated with natalizumab developed progressive multifocal leukoencephalopathy.

Overall, 4 deaths were recorded during the follow-up period - 3 in the natalizumab group and 1 in the AHSCT group (including 3 patients with secondary and 1 with primary progressive MS; 5, 8, 8 and 9 years after the initiation of study therapy). The causes of death included 3 instances

of infectious and cardiovascular complications of advanced disability, and a case of pulmonary fibrosis. None of the deaths were related to the study therapy.

Table 2
Serious adverse events reported after AHSCT

serious adverse event	number of events
Infections	
herpes simplex or zoster	7
cytomegalovirus	4
Epstein-Barr virus	1
other viral infection	1
bacterial infection	2
upper respiratory tract infection	3
lower respiratory tract infection	1
pyelonephritis	2
lower urinary tract infection	2
vaginitis	1
Haematological	
febrile neutropenia	3
serum sickness	9
pulmonary embolism	1
thrombocytopenia	1
neutropenia (late)	1
Gastrointestinal	
clostridium colitis	1
giardiasis	1
Endocrinological	
hypothyroidism	2
ovarian failure	1
Anorexia nervosa	1
Other	2

DISCUSSION

This study used composite data from 7 expert AHSCT MS centres and the international MSBase registry to emulate a trial of comparative effectiveness of AHSCT with natalizumab in progressive forms of MS. The choice of natalizumab as a negative comparator therapy was motivated by the fact that it did not show effect on a composite disability outcome in secondary progressive MS in the ASCEND trial – including in a subgroup that presented with Gd-contrast-

enhancing lesions at trial baseline.[11] In the present study, AHSCT and natalizumab were mainly used off-label as rescue therapies in attempts to ameliorate progression or, in a small number of cases, eliminate relapses in progressive MS. In 39 patients treated with AHSCT matched with 65 patients treated with natalizumab, we found no evidence of difference in the probability of disability worsening, disability improvement or the risk of relapse. The study was powered to identify large treatment effects, which would be required to justify clinical use of AHSCT in people with progressive MS given the significant adverse effects profile of AHSCT. Indeed, adverse events related to AHSCT were observed in most of the treated patients. Reassuringly, no treatment-related death was reported.

It would be conceivable that patients with active progressive MS, who also had experienced a relapse during the preceding 2 years, would potentially benefit more from AHSCT in comparison with natalizumab - similar to the observation in relapsing-remitting MS.[3] However, even though half of our present study cohort had experienced a relapse during the preceding 2 years, the study did not find any difference in the effectiveness of the two therapies either on the disability or, notably, on relapse outcomes.

Only a limited information is presently available to guide the use of AHSCT among patients with progressive MS. A study from the BMT-MS Study Group and the Italian MS Register described superiority of AHSCT at preventing and reducing disability among 79 patients with secondary progressive MS matched with patients treated with other therapies. Because the comparator group combined low- and high-efficacy disease modifying therapies as well as immunosuppressants, the study did not answer the question whether the effectiveness of AHSCT is superior to a single high-efficacy immunotherapy. In the Italian study, the included patients were experiencing a highly inflammatory phenotype of secondary progressive MS, with pre-baseline ARR of 0.9-1.01. This is almost twice the frequency of relapses observed in our study cohort and represents the most likely explanation of the reported benefit of AHSCT.[35] On the other hand, a single-centre cohort study from Florence did not suggest any superior effect of AHSCT on disability worsening or improvement when compared with cyclophosphamide in 31

and 62 matched patients.[5] The pre-baseline relapse frequency in the Florence cohort was 0.46-0.56, comparable to our cohort presented here. This observation is corroborated by an experience from 62 patients with progressive MS treated with AHSCT at 2 expert centres in London, of whom 56 presented with radiological activity in the year preceding treatment, with the average of 0.25 relapses per year. The mean rate of EDSS change was +0.11 steps before the treatment and +0.24 steps within the year following AHSCT. Two patients died in relation to AHSCT.[36]

It is worth mentioning that a small phase 2 trial compared a mixed group of 9 patients with relapsing or progressive MS treated with myeloablative AHSCT with 12 patients treated with mitoxantrone. The trial concluded that AHSCT was more effective than mitoxantrone in reducing clinical and radiological evidence of MS activity, but with no observed difference in disability outcomes.[37]

Randomised trials of AHSCT in progressive MS are lacking. Only one phase 3 randomised controlled trial is presently enrolling participants with progressive MS alongside participants with relapsing MS (www.clinicaltrials.gov, accessed 8/7/2023). The BEAT-MS trial (US, NCT04047628) is comparing the efficacy of AHSCT against a composite group of best available therapies among patients who experienced at least 2 relapses of MS during the preceding 3 years. This trial will enrol 156 participants and upon its scheduled completion in 2029 will provide information about comparative efficacy of AHSCT among patients with highly active relapsing or progressive disease. However, the BEAT-MS trial will not study the effect of AHSCT among patients with prominently progressive MS phenotype.

Natalizumab is an antitrafficking agent that prevents recruitment of lymphocytes from the circulation into the CNS. Through this reduction of ingress of immune cells, it modifies the autoimmune cascades compartmentalised behind the blood-brain barrier. Similarly, the effect of AHSCT conditioning is exerted mainly on the circulating immune system, lymphatic tissue and bone marrow. It is therefore conceivable that the low-intensity autoimmune processes

within the CNS or other processes implicated in the worsening of disability in progressive MS may remain relatively unaffected by AHSCT as well as natalizumab.[38]

Consistent with the previous reports, most patients who received AHSCT experienced adverse events potentially associated with treatment, among which infectious complications were the most common. The proportion of patients requiring ICU admission (15%) was higher than what would be expected in a less disabled cohort with relapsing-remitting MS, but only 7.6% experienced febrile neutropenia.[3] Reassuringly, no treatment-related mortality was reported.

The main limitations of this study are the lack of randomisation and the relatively small sizes of the compared treatment groups. However, given the considerable difficulties in conducting an appropriately blinded randomised controlled trial of AHSCT among patients with prominently progressive MS forms, rigorously conducted analysis of the available observational data represents the most suitable solution to generating this essential information. The study design and statistical methodology were used to emulate a target trial according to an accepted procedure.[18] Our ability to optimally balance the compared groups was limited by the small number of eligible patients. The residual imbalance in age, time from MS onset and year at baseline was therefore mitigated by additional adjustment of the inferential models.[39] To account for regional differences in the use of AHSCT, matching included geographic region. Analyses were also adjusted for frequency of clinical assessments to mitigate detection bias. The limited duration of the pairwise-censored on-treatment follow-up allowed this study to only evaluate disability outcomes over the short-term. Due to the incomplete safety data in the natalizumab group, this study did not compare safety between AHSCT and natalizumab. Thus, the full evaluation of the long-term risk-benefit profile of AHSCT in progressive MS will depend on future randomised trials with extended follow-up. On the other hand, systematically recorded short- and long-term safety data were available in the AHSCT group. Importantly, no treatment-related deaths or progressive multifocal leukoencephalopathy were observed in either studied group. Whether conventional disease modifying therapies with successful phase 3 randomised controlled trials in progressive MS, such as ocrelizumab and siponimod, offer an

advantage over AHSCT in this scenario represents further interesting research question. More data from patients with progressive MS treated with ocrelizumab or siponimod will be required before it can be answered.

In this study, we show that over the median of 2 years and up to 4 years, AHSCT is not superior to natalizumab in reducing the risk of disability worsening and increasing the chance for disability improvement among patients with progressive MS with low level of relapse activity. Given the previously reported lack of effect of natalizumab on disability worsening in secondary progressive MS, our study provides no evidence in support of the effectiveness of AHSCT on disability in this setting. Even though the study was not powered to identify small-to-moderate magnitudes of treatment effect, such effects of AHSCT on disability would not be of sufficient clinical importance to justify its use in progressive MS, given its intensity and the risk of treatment-related adverse events. Therefore, the results of the present study do not support standard use of AHSCT in progressive MS with low level of episodic focal inflammatory activity. In addition to its clinical implications, this study also suggests that future randomised trials of AHSCT should preferentially include patients with highly active MS.[35]

ACKNOWLEDGMENTS

The list of MSBase Study Group co-investigators and contributors is given in Table S1. We thank the MSBase Operations team Charlotte Sartori, Eloise Hinson, Pamela Farr, Rein Moore, Dusko Stupar, Cynthia Tang and Sonya Smirnova. 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 MSBase sponsors.

Funding statement

This research was funded in part by the National Health and Medical Research Council [1129189, 2026836] and Multiple Sclerosis Australia [19-800]. For the purposes of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Authors' contributions

Tomas Kalincik conceptualised and designed the study, recruited patients, contributed data, carried out statistical analysis, interpreted the results, have drafted and edited the manuscript.

Jennifer Massey, Ian Sutton, Barbara Withers, Mark S. Freedman, Harold Atkins, Eva Krasulova, Eva Kubala Havrdova, Marek Trneny, Tomas Kozak, Joachim Burman, Richard Macdonell, Øivind Torkildsen, Lars Bø, Basil Sharrack, John Snowden conceptualised the study, recruited patients, contributed data, interpreted the results and have edited the manuscript. Sifat Sharmin, Izanne Roos interpreted the results and have edited the manuscript.

POTENTIAL 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.
Sifat Sharmin has nothing to disclose.
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.
Barbara Withers has nothing to disclose.
Mark S. Freedman has nothing to disclose.
Harold Atkins has nothing to disclose.
Eva Kubala Havrdova received honoraria/research support from Biogen, Merck Serono, Novartis, Roche, and Teva; 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.
Eva Krasulova has nothing to disclose.
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.
Tomas Kozak has nothing to disclose.
Joachim Burman has nothing to disclose.
Richard Macdonell received compensation for traveling, conference fees and consulting fees from Merck, Teva, Sanofi Genzyme, Biogen Idec, Novartis, Roche, BMS, Celgene.
Oivind Torkildsen received speaker honoraria from and served on scientific advisory boards for Biogen, Sanofi-Aventis, Teva, Merck and Novartis.
Lars Bo received speaker honoraria from Novartis, and consultant fees from Viatris.
Anne Kristin Lehmann did not declare any disclosures.
Basil Sharrack has nothing to disclose.
John Snowden declares honoraria for educational events from Jazz, Gilead, Janssen, for advisory board membership from Medac and Vertex, and for trial IDMC membership from Kiadis Pharma.

PATIENT AND PUBLIC INVOLVEMENT

This is a retrospective analysis of registry data. Therefore, an a-priori consultation of patients and public regarding the design of the study and use of the source data was

not possible. However, AHSCT has been repeatedly identified by consumers as an intervention of high interest in the treatment of multiple sclerosis.

DATA SHARING STATEMENT

The data are the property of the individual centres. Data from the participating cohorts can be requested from the principal investigators, at their discretion and conditional on 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.

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FIGURE LEGENDS

Figure 1
Consort diagram of patient disposition

AHSCT, autologous hematopoietic stem cell transplantation; CIS, clinically isolated syndrome; MS, multiple sclerosis

Figure 2
Visualisation of balance between the compared treatment groups before (yellow circles) and after (green rhombi) matching on the measured variables

low-efficacy therapies: interferons β, glatiramer acetate, teriflunomide;
medium-efficacy therapies: dimethyl fumarate, fingolimod, cladribine;
high-efficacy therapies: natalizumab, alemtuzumab, ocrelizumab, rituximab. mitoxantrone;EDSS, Expanded Disability Status Scale

Figure 3
Comparison of disability outcomes between the matched AHSCT and natalizumab groups

The cumulative hazard functions of multiple outcome events illustrate the analysis of repeated outcomes carried out with Andersen-Gill proportional hazards models. The inset shows the proportions of patients who had experienced an outcome event at years 2 and 4.

AHSCT, autologous hematopoietic stem cell transplantation; 95%CI, 95% confidence interval

Figure 4
Comparison of relapse outcomes between the matched AHSCT and natalizumab groups

The cumulative hazard functions of multiple outcome events illustrate the analysis of repeated outcomes carried out with Andersen-Gill proportional hazards models. The inset shows the proportions of patients who had experienced a relapse at years 2 and 4.
AHSCT, autologous hematopoietic stem cell transplantation; 95%CI, 95% confidence interval