Comparative effectiveness of autologous hematopoietic stem cell transplant vs Fingolimod, Natalizumab, and Ocrelizumab in highly active relapsing-remitting multiple sclerosis

Title :

Effectiveness of autologous haematopoietic stem cell transplantation versus fingolimod, natalizumab and ocrelizumab in highly active relapsing-remitting multiple sclerosis

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KEY POINTS

Question

The evidence regarding the effectiveness of autologous haematopoietic stem cell transplantation (AHSCT) is limited. We have conducted a literature search using the PubMed database, with search terms “haematopoietic stem cell transplantation” AND “relapsing-remitting multiple sclerosis” AND “disease modifying therapy” AND “trial” published between 1/1/1990 and 1/10/2022 in any language. Only two randomised clinical trials were identified. In one trial, AHSCT used in 9 patients with relapsing or progressive multiple sclerosis was superior to mitoxantrone in reducing clinical or radiological episodic inflammatory activity. In another trial, AHSCT used in 55 patients with relapsing-remitting multiple sclerosis was superior to a mixed group of various therapies in controlling relapses and disability. Presently, information about the effectiveness of AHSCT in comparison to individual most potent disease modifying therapies for relapsing-remitting multiple sclerosis, such as natalizumab or ocrelizumab, is lacking.

Findings

This observational study, utilising a composite cohort from specialised MS centres and the MSBase international registry, compares the effectiveness of AHSCT to one medium-efficacy and two high-efficacy disease modifying therapies – fingolimod, natalizumab and ocrelizumab – in patients with relapsing-remitting multiple sclerosis, high frequency of relapses and moderate disability. It shows that AHSCT is substantially superior to fingolimod and marginally superior to natalizumab in preventing relapses over 5 years. AHSCT is also associated with a higher rate of recovery from disability in comparison to fingolimod and natalizumab. With a shorter follow-up of 3 years, the study found no evidence of difference in clinical outcomes between AHSCT and ocrelizumab. Complications of AHSCT are common. One treatment-related death was reported among the 159 AHSCT-treated patients with relapsing remitting MS.

Meaning

The results of the present study indicates that the use of AHSCT is justified among patients with highly active relapsing-remitting multiple sclerosis, especially those presenting with relapses despite being treated with highly effective disease modifying therapies.

ABSTRACT

Importance: Autologous hematopoietic stem cell transplantation (AHSCT) is available for treatment of highly active multiple sclerosis (MS). So far, no randomised controlled trials have compared the efficacy of AHSCT to individual high-efficacy disease modifying therapies.

Objective: This study emulated pairwise trials of comparative effectiveness of AHSCT vs. fingolimod, natalizumab and ocrelizumab (registration nr. ACTRN12605000455662).

Design: Observational cohort/registry study of comparative treatment effectiveness over 3-5 years between 2006-2021.

Setting: 6 specialist MS centres with AHSCT programs and international MSBase registry.

Participants: The study included patients with relapsing-remitting MS treated with AHSCT (n=167) or fingolimod (n=2558), natalizumab (n=1490) or ocrelizumab (n=700) and sufficient on-treatment follow-up including disability assessments. The patients 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.

Exposure: AHSCT or fingolimod, natalizumab, ocrelizumab.

Main outcomes: The pairwise-censored groups were compared on annualised relapse rates (ARR) and freedom from relapses and 6-month confirmed EDSS worsening and improvement.

Results: The matched study groups were 65-70% women, of mean age 35-37, mean disease duration of 8-9 years, average EDSS 3.5-4 and high frequency of relapses (mean 0.77-0.86) in the preceding year. In comparison to fingolimod (n=769), AHSCT (n=144) was associated with fewer relapses (ARR: mean±SD 0.09±0.30 vs. 0.20±0.44), similar risk of EDSS worsening (HR=1.70, 95%CI=0.91-3.17) and higher chance of disability improvement (HR=2.70, 95%CI=1.71-4.26) over 5 years. Compared to natalizumab (n=730), AHSCT (n=146) was associated with marginally lower ARR (0.08±0.31 vs. 0.10±0.34), similar risk of EDSS worsening (HR=1.06, 95%CI=0.54-2.09), and higher chance of EDSS improvement (HR=2.68, 95%CI=1.72-4.18) over 5 years. AHSCT (n=110) and ocrelizumab (n=343) were associated with similar ARR (0.09±0.34 vs. 0.06±0.32), EDSS worsening (HR=1.77, 95%CI=0.61-5.08) and EDSS improvement (HR=1.37, 95%CI=0.66-2.82) over 3 years. AHSCT-related mortality occurred in 1 of 159 patients (0.6%).

Conclusion: In highly active relapsing-remitting MS, AHSCT is considerably superior to fingolimod and marginally superior to natalizumab in preventing relapses and facilitating recovery from disability. This study did not find evidence for difference in the effectiveness of AHSCT and ocrelizumab over a shorter available follow-up time.

TEXT

INTRODUCTION

Chemotherapy followed by autologous hematopoietic stem cell transplantation (AHSCT) is a potent immunosuppressant/immune-reconstitution therapy that is occasionally used to treat highly inflammatory multiple sclerosis (MS) with suboptimal response to conventional disease modifying therapies (DMT). As a result of ablation and subsequent reconstitution of the immune system, it is particularly effective in temporarily eliminating neuroinflammation within the central nervous system.[1] Single-arm cohort studies reported prolonged freedom from relapses and worsening of disability in aggressive MS post-AHSCT.[2-6] Only one open-label randomised trial compared the efficacy of AHSCT with a combination of DMT and non-DMT interventions in relapsing-remitting MS.[7]

AHSCT is associated with significant risks, including early complications of immune ablation and 0.3-2% treatment-related mortality.[1,8] The risk of death has declined over the recent years, mainly as a result of improved patient selection and transplant centre experience.[9] AHSCT therefore represents a higher-risk but potentially higher-yield therapy with long-term benefit. However, to define the role of AHSCT in active MS, we need to understand its comparative effectiveness relative to the most effective available DMTs. High-quality cohorts have helped establish the comparative effectiveness among DMTs.[10-15] Emulation of clinical trials in existing datasets supports treatment decisions, especially where randomised trials would not be feasible.[16,17] A scenario ideally suited to this approach is a comparison of AHSCT with high-efficacy DMTs.[18,19]

In this study, we emulated a clinical trial that compared clinical effectiveness of AHSCT with two high-efficacy DMTs (natalizumab, ocrelizumab) and one moderate-efficacy DMT (fingolimod).

METHODS

Patients and data

Data, recorded between 2006-2021, were obtained from 6 cohorts treated with AHSCT at specialised centres (in Ottawa, Uppsala, Sheffield, Bergen, Sydney and Melbourne) and 94 centres in 27 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 definite relapsing-remitting MS,[20-22] first exposure to one of the study therapies, no exposure to alemtuzumab or participation in randomised clinical trials within the prior 10 years, minimum recorded follow-up 2 months prior to treatment start and 2 post-baseline disability scores (including ≥1 on treatment), persistence on study therapy for ≥1 month 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 consecutive patients treated with AHSCT were included.

Procedures

Patients received AHSCT following protocols specific to the treating centres.[2,3,5,23] 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. Infection prophylaxis was used as per local protocols.

The patients included in the DMT arms were treated either with fingolimod (0.5mg oral daily), ocrelizumab (600mg IV every 6 months) or natalizumab (300μg IV every 4 weeks). Baseline was defined as the first day of AHSCT conditioning or commencement of the DMT. Patients were censored at discontinuing therapy (with the minimum duration of treatment effect set at 60 days after starting fingolimod or natalizumab, 6 months after ocrelizumab, and 5 years after AHSCT),[24] commencing another DMT, or at the last recorded disability score, whichever occurred first.

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, but patients with less frequent visits were not excluded.[25] Data from different sources were mapped, combined and underwent a rigorous quality procedure (eTable 2).[26]

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.[27] Confirmation of relapses by Expanded Disability Status Scale (EDSS) was not mandated. Individual ARR between baseline and censoring was calculated.

Secondary endpoints were the cumulative hazards of first post-baseline relapse, the proportions of patients free from disability worsening and with disability improvement. Disability was scored by EDSS scorers (Neurostatus certification was required 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.[28]

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

Statistical analysis

This study emulated three clinical trials comparing AHSCT with fingolimod, natalizumab and ocrelizumab (eTable 3).[29] Matching and statistical analyses were conducted using R (v4.1.1).[30] Individual patients were matched on their propensity of receiving either of the compared therapies in 1:10 variable matching ratio without replacement within a caliper of 0.1 standard deviations of the propensity score. Individual propensity scores were calculated using a multivariable logistic model of treatment allocation that utilised demographic and clinical variables available 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). The pairwise-censored on-treatment follow-up was determined in each matched pair as the shorter of the two patient follow-up periods, to mitigate attrition bias, informative censoring and the effect of differential treatment persistence.[12]

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) adjusted for visit frequency and with robust estimation of variance. Interaction term for treatment and time was introduced in the models where Schoenfeld's global test indicated violation of the proportionality of hazards assumption.

Robustness of the statistically significant differences to unidentified confounders was quantified with Hodges-Lehmann Γ.[31] 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

A total of 167 (AHSCT), 2558 (fingolimod), 1490 (natalizumab), and 700 (ocrelizumab) patients fulfilling the inclusion criteria were identified (Figure 1, eTable 4). Among the AHSCT cohort, the conditioning intensity was used as follows: high-intensity in 43 patients (26%), intermediate-intensity myeloablative in 49 patients (29%), intermediate-intensity lymphoablative in 64 patients (38%) and low- to intermediate-intensity in 11 patients (7%).[19] As expected, the four unmatched groups differed in their baseline characteristics (eTable 5). From the logistic models used to derive the propensity scores, it is apparent that patients tended to commence AHSCT at younger age, higher disability, and shorter disease duration compared to the three studied DMTs (eTable 6).

Effectiveness

The numbers of patients retained in the three pairwise matched comparisons are shown in Table 1. The matching procedure significantly decreased the differences in propensity scores between the compared groups from 0.35-0.41 to 0.002-0.005, corresponding to a 99.0-99.5% improvement in the overall balance. The close match on individual characteristics is demonstrated in Table 1 (standardised differences ≤10% for all matched characteristics). As a result of pairwise censoring, on-treatment follow-up was identical in the matched groups. The groups were not matched on the between-visit intervals, for which the analyses were then adjusted.

Patients treated with AHSCT experienced fewer relapses than those treated with fingolimod (Figure 2; ARR, mean±standard deviation [SD] 0.09±0.30 vs. 0.20±0.44, respectively, p<0.0001). This observation was robust to unmeasured confounding (Γ>100%) and confirmed by the cumulative hazard of relapse (hazard ratio [HR]=0.26, 95% confidence interval [95%CI]=0.18-0.36). We did not find evidence for difference in the cumulative hazards of 6-month confirmed disability worsening over up to 5 years (HR=1.70, 95%CI=0.91-3.17). AHSCT was superior in facilitating 6-month confirmed improvement of disability than fingolimod (HR=2.70; 95%CI=1.71-4.26).

The ARR in the AHSCT group was marginally lower than in the natalizumab group (Figure 3; 0.08±0.31 vs. 0.10±0.34, respectively, p=0.03), as also confirmed by the cumulative hazard of relapses (HR=0.51, 95%CI=0.34-0.74). This observation was moderately robust to unmeasured confounding (Γ=20%). The study did not find evidence for difference in the 6-month confirmed disability worsening between AHSCT and natalizumab (HR=1.06, 95%CI=0.54-2.09), with similar proportions of patients who experienced disability worsening by years 2 and 5. AHSCT was superior in facilitating 6-month confirmed improvement of disability consistently during the 5-year follow-up (HR=2.68; 95%CI=1.72-4.18).

The analysable follow-up for ocrelizumab was relatively shorter, up to 3 years from commencing study therapy. The risk of relapses was similar in the AHSCT and the ocrelizumab groups, as demonstrated by ARR (Figure 4; 0.09±0.34 vs. 0.06±0.32, respectively, p=0.86) and cumulative hazard of relapses (HR=0.75, 95%CI=0.36-1.57). This observation was moderately robust to potential unmeasured confounding (Γ=40%). The cumulative hazards and the proportions of patients who remained free from 6-month confirmed disability worsening (HR=1.77, 95%CI=0.61-5.08) and experienced 6-month confirmed disability improvement (HR=1.37, 95%CI=0.66-2.82) were similar.

According to the power analysis, the emulated trials were sufficiently powered to detect minimum differences of 0.17 relapses per year and 19-69% of the cumulative hazards of outcome events (eTable 7).

Safety

Safety data were available for the patients treated with AHSCT. Among the 159 patients who were matched in at least one of the pairwise analyses, 37 patients experienced febrile neutropenia during mobilisation, 18 patients experienced serum sickness, and 14 patients required ICU admission. 82 serious adverse events were recorded in 58 patients after discharge post-AHSCT, these consisted mainly of infections (49), especially of viral aetiology (34; eTable 8). Treatment-related death was reported in one patient (0.6%, due to veno-occlusive disease of the liver post-busulfan).

DISCUSSION

We have used composite data from 6 AHSCT centres and the international MSBase registry to emulate comparative trials of AHSCT vs. two high-efficacy and one medium-efficacy disease modifying therapies for MS. The results showed that AHSCT is highly efficacious when used to treat highly active relapsing-remitting MS. Its ability to prevent relapses is substantially superior to fingolimod, marginally superior to natalizumab, and, with a shorter follow-up, appears similar to ocrelizumab. The study did not find evidence for a difference in the probability of disability worsening between AHSCT and the comparator DMTs, and in the probability of disability improvement over a shorter available follow-up between AHSCT and ocrelizumab. AHSCT is associated with a higher rate of recovery from disability in comparison to fingolimod and natalizumab, especially during the initial year post-treatment, when it was observed among approximately 30% of the patients treated with AHSCT. This is of particular interest, as natalizumab is associated with a particularly high (25%) probability of confirmed reduction of neurological disability shortly after its commencement.[12,32]

To date, only two randomised controlled trials of AHSCT have been completed. A 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 episodic

inflammatory activity.[33] The phase 3 MIST trial compared 55 patients with relapsing-remitting MS randomised to non-myeloablative AHSCT with the same number randomised to escalation of DMT.[7] The trial reported superiority of AHSCT in reducing the risk of disability worsening, relapses and MRI activity. Because the interventions in the DMT escalation group ranged from interferon β to natalizumab with or without add-on methylprednisolone, rituximab, plasmapheresis, cyclophosphamide or intravenous immunoglobulins, the study did not generate evidence regarding the effectiveness of AHSCT head-to-head with the most potent available DMTs.

Presently, three randomised clinical trials comparing AHSCT (cyclophosphamide-ATG protocols) to composite comparator groups treated with specific high-efficacy DMTs in highly active MS are underway.[8] The RAM-MS trial (phase 3, Scandinavia, Netherlands) will compare the efficacy of AHSCT against alemtuzumab, ocrelizumab and cladribine. The STAR-MS trial (phase 3, UK) uses a composite comparator group of alemtuzumab, ocrelizumab and cladribine. The COAST trial (phase 2, Germany) compares AHSCT versus a composite comparator of ocrelizumab or alemtuzumab. In addition, two randomised trials are comparing AHSCT with BEAM-ATG conditioning against a range of high-efficacy DMTs representing the best standard care: BEAT-MS (phase 3, US) and NET-MS (phase 2, Italy). These trials will generate important evidence to guide the use AHSCT in the future. Their results are expected to become available over the next decade.

Our present study enables us to draw conclusions separately about the effectiveness of AHSCT vs. two high-efficacy and one medium-efficacy DMT among patients with highly active relapsing-remitting MS. The cohort represents typical clinical scenarios in which AHSCT is presently considered – highly inflammatory disease in young patients with prior failures of potent DMTs and mild-moderate disability. With the comparison of AHSCT against fingolimod we have established discriminative ability of the matched analysis, clearly demonstrating the expected superiority of AHSCT. In comparison to natalizumab, AHSCT was marginally superior at reducing relapse activity over 5 years (absolute difference of 1 relapse per 50 patient-years). In none of the comparisons did the superior effect of AHSCT translate into reducing the risk of disability worsening. On the other hand, AHSCT was associated with partial recovery from the previously accumulated neurological disability when compared with fingolimod and natalizumab. Interestingly, we did not find evidence of difference between the effects of AHSCT and ocrelizumab on relapses, studied over a shorter, 3-year follow-up. The observation that AHSCT showed superiority in clinical outcomes over fingolimod and, to a lesser extent, natalizumab, but not ocrelizumab, is intriguing. While this may be attributed to the shorter on-treatment follow-up available in the ocrelizumab cohort, another explanation may relate to the differences in the mechanisms of action among the therapies. Fingolimod and natalizumab are antitrafficking agents, sequestrating lymphocytes outside of the CNS, whereas ocrelizumab acts through depletion of CD20-positive cells – a mechanism that is more similar to the immunosuppressive effect of AHSCT.[34]

The safety profile of AHSCT is consistent with the previous cohort experience. A considerable number of patients experienced febrile neutropenia during mobilisation with cyclophosphamide and 9% required ICU admission. Doses lower than $2g/m^2$ are associated with a lower risk of this complication. Whether the lymphodepleting effect of cyclophosphamide is dose-dependent and whether the mononuclear content of the graft impacts on the outcome is unknown. Almost one third of patients developed infectious complications at later stages, following recovery from the transplant procedures. Only one treatment-related death (0.6%) was reported.

The main limitation of this study is its lack of true randomisation. However, randomisation to AHSCT or DMT with appropriate blinding is extremely problematic, given the considerably different intensities of treatment protocols, persistence and safety profiles.[35] It has therefore been argued that observational data analysed with appropriate statistical methodology represent an optimal solution to establishing evidence for comparative effectiveness of AHSCT.[36] We have utilised well-established methods to emulate clinical trials using a large composite database of patients treated with AHSCT or DMTs, and this provides this study with larger power and generalisability than the previous randomised trials.[17] We have applied matching, pairwise censoring and model adjustment to mitigate the potential biases, an approach whose validity was demonstrated in our previous studies.[12,37] 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 study did not allow direct comparison of the safety for AHSCT and the DMTs, the systematic acquisition of safety information in the AHSCT cohort enabled us to report short- and long-term safety outcomes of AHSCT. Because MRI information was unavailable in more than half of the AHSCT cohort, this study 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. Our previous studies did not show any effect of inclusion of MRI in matching on their results.[11,12] To account for geographic differences in cohorts and outcomes,[38] 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, we have adjusted models for the frequency of visits with EDSS scores. To explore the specific effectiveness of conditioning regimens on the effectiveness of AHSCT, a dedicated study with specific design will be required.

We show that over 5 years, the effect of AHSCT on suppressing relapses and facilitating recovery from disability in highly active relapsing-remitting MS is superior to fingolimod and natalizumab. Even though it requires a complex treatment procedure, its one-off nature may offer practical advantages over the continuously administered therapies.[8] AHSCT is associated with considerable risks, but the risk of treatment-associated mortality is low. AHSCT is highly effective disease modifying therapy suitable for those with highly inflammatory relapsing-remitting MS.

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The list of MSBase Study Group co-investigators and contributors is given in eTable 1.
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.
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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. Mark S. Freedman, Harold Atkins, Joachim Burman, Jennifer Massey, Ian Sutton, Barbara Withers, Richard Macdonell, Andrew Grigg, Oivind Torkildsen, Lars Bo, Anne Kristin Lehmann, 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. Eva Kubala Havrdova, Eva Krasulova, Marek Trneny, Tomas Kozak, Anneke van der Walt, Helmut Butzkueven, Pamela McCombe, Olga Skibina, Jeannette Lechner-Scott, Barbara Willekens, Elisabetta Cartechini, Serkan Ozakbas, Raed Alroughani, Jens Kuhle, Francesco Patti, Pierre Duquette, Alessandra Lugaresi, Samia J. Khoury, Mark Slee, Recai Turkoglu, Suzanne Hodgkinson, Nevin John, Davide Maimone, Maria Jose Sa; Vincent van Pesch, Oliver Gerlach, Guy Laureys, Liesbeth Van Hijfte, Rana Karabudak, Daniele Spitaleri, Tunde Csepany, Riadh Gouider, Saloua Mrabet, Tamara Castillo Triviño, Justin Garber, Jose Luis Sanchez-Menoyo, Eduardo Aguera-Morales, Yolanda Blanco, Abdullah Al-Asmi, Bianca Weinstock-Guttman, Bruce Taylor, Yara Fragoso, Koen de Gans, Allan Kermode recruited patients, contributed data, interpreted the results and have edited the manuscript.

DATA SHARING STATEMENT

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.

DECLARATION OF INTERESTS

Tomas Kalincik served on scientific advisory boards for 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, 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.
Mark Freedman received research/educational grants from Sanofi-Genzyme Canada, honoraria/consultation fees from Alexion, Atara Biotherapeutics, Bayer Healthcare, Beigene, BMS (Celgene), EMD Inc., Hoffman La-Roche, Janssen (J&J), Merck Serono, Quanterix, Novartis, Sanofi-Genzyme, Teva Canada Innovation. He served as a member of company advisory boards or boards of directors for Alexion, Atara Biotherapeutics, Bayer Healthcare, Beigene, BMS (Celgene), Celestra Health, Hoffman La-Roche, Janssen (J&J), McKesson, Merck Serono, Novartis, Sanofi-Genzyme and participated in company sponsored speaker's bureau for Sanofi-Genzyme and EMD Serono.
Harold Atkins has nothing to disclose.
Joachim Burman has nothing to disclose.
Ian Sutton received compensation for an educational activity from Biogen.
Barbara Withers has nothing to disclose.
Jennifer Massey served on scientific advisory board for Roche, received conference travel support and/or speaker honoraria from Novartis, Biogen, Roche and Merck.
Richard Macdonell received compensation for traveling, conference fees and consulting fees from Merck, Teva, Sanofi Genzyme, Biogen Idec, Novartis, Roche, BMS, Celgene.
Andrew Grigg has nothing to disclose.
Oivind Torkildsen received speaker honoraria from and served on scientific advisory boards for Biogen, Sanofi-Aventis, Merck and Novartis.
Lars Bo received speaker honoraria from Novartis, and consultant fees from Viatris.
Anne Kristin Lehmann did not declare any disclosures.
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; has been supported by the Czech Ministry of Educaon research project PROGRES Q27/LF1.
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.
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, F. Hoffmann-La Roche Ltd, Merck, Alexion, CSL, and Novartis; has carried out contracted research for Novartis, Merck, F. Hoffmann-La Roche Ltd and Biogen; has taken part in speakers' bureaus for Biogen, Genzyme, UCB, Novartis, F. Hoffmann-La Roche Ltd and Merck; has received personal compensation from Oxford Health Policy Forum for the Brain Health Steering Committee.
Pamela McCombe received speaker fees and travel grants from Novartis, Biogen, T'évalua, Sanofi
Olga Skibina has nothing to disclose.
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, TEVA and Novartis.
Barbara Willekens received honoraria for acting as a member of Scientific Advisory Boards for Almirall, Biogen, Celgene/BMS, Merck Serono, Novartis, Roche, Sanofi-Genzyme and speaker honoraria and travel support from Biogen, Merck Serono, Novartis, Roche, Sanofi-

Genzyme; research and/or patient support grants from Roche, Biogen, Merck-Serono, Sanofi-Genzyme. Honoraria and grants were paid to UZA/UZA Foundation.
Elisabetta Cartechini has nothing to disclose.
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Serkan Ozakbas has nothing to disclose.
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Jens Kuhle received speaker fees, research support, travel support, and/or served on advisory boards by Swiss MS Society, Swiss National Research Foundation (320030_189140/1), Progressive MS Alliance, Bayer, Biogen, Bristol Myers Squibb, Celgene, Merck, Novartis, Octave Bioscience, Roche, Sanofi.
Francesco Patti received speaker honoraria and advisory board fees from Almirall, Bayer, Biogen, Celgene, Merck, Novartis, Roche, Sanofi-Genzyme and TEVA. He received research funding from Biogen, Merck, FISM (Fondazione Italiana Sclerosi Multipla), Reload Onlus Association and University of Catania.
Pierre Duquette served on editorial boards and has been supported to attend meetings by EMD, Biogen, Novartis, Genzyme, and TEVA Neuroscience. He holds grants from the CIHR and the MS Society of Canada and has received funding for investigator-initiated trials from Biogen, Novartis, and Genzyme.
Alessandra Lugaresi has received personal compensation for consulting, serving on a scientific advisory board, speaking or other activities from Roche, Biogen, Bristol Myers Squibb, Merck Serono, Mylan, Novartis, Roche, Sanofi/Genzyme, Teva. Her institutions have receved research grants from Novartis and Sanofi [].
Bassem Yamout has nothing to disclose.
Samia J. Khoury received compensation for serving on scientific advisory boards from Roche and Merk.
Mark Slee has participated in, but not received honoraria for, advisory board activity for Biogen, Merck, Bayer Schering, Sanofi Aventis and Novartis.
Recai Turkoglu has nothing to disclose.
Suzanne Hodgkinson received honoraria and consulting fees from Novartis, Bayer Schering and Sanofi, and travel grants from Novartis, Biogen Idec and Bayer Schering.
Nevin John is a local principal investigator on commercial studies funded by Novartis, Biogen, Amicus and Sanofi.
Davide Maimone received speaker honoraria for Advisory Board and travel grants from Almirall, Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and Teva.
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Vincent van Pesch received travel grants from Merck Healthcare KGaA (Darmstadt, Germany), Biogen, Sanofi, Bristol Meyer Squibb, Almirall and Roche. His institution has received research grants and consultancy fees from Roche, Biogen, Sanofi, Merck Healthcare KGaA (Darmstadt, Germany), Bristol Meyer Squibb, Janssen, Almirall and Novartis Pharma
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Jose Luis Sanchez-Menoyo accepted travel 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
Eduardo Aguera-Morales has nothing to disclose.
Yolanda Blanco has nothing to disclose.
Abdullah Al-Asmi has nothing to disclose.
Bianca Weinstock-Guttman has participated in speaker's bureaus and/or served as a consultant for Biogen, EMD Serono, Novartis, Genentech, Celgene/Bristol Meyers Squibb, Sanofi Genzyme, Bayer, Janssen and Horizon. Dr Weinstock-Guttman also received grant/research support from the agencies listed above.
Bruce Taylor received funding for travel and speaker honoraria from Bayer Schering Pharma, CSL Australia, Biogen and Novartis, and has served on advisory boards for Biogen, Novartis, Roche and CSL Australia.
Yara Fragoso received honoraria as a consultant on scientific advisory boards by Novartis, Teva, Roche and Sanofi-Aventis and compensation for travel from Novartis, Biogen, Sanofi Aventis, Teva, Roche and Merck.
Koen de Gans has nothing to disclose.
Allan Kermode received speaker honoraria and scientific advisory board fees from Bayer, BioCSL, Biogen, Genzyme, Innate Immunotherapeutics, Merck , Novartis, Sanofi, Sanofi-Aventis, and Teva.
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John Snowden declares honoraria for educational events from Novartis, Jazz, Gilead, Janssen, for advisory board membership from Medac, and for trial IDMC membership from Kiadis Pharma.

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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

Comparative effectiveness of AHSCT and fingolimod

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

Figure 3

Comparative effectiveness of AHSCT and natalizumab

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

Figure 4

Comparative effectiveness of AHSCT and ocrelizumab

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

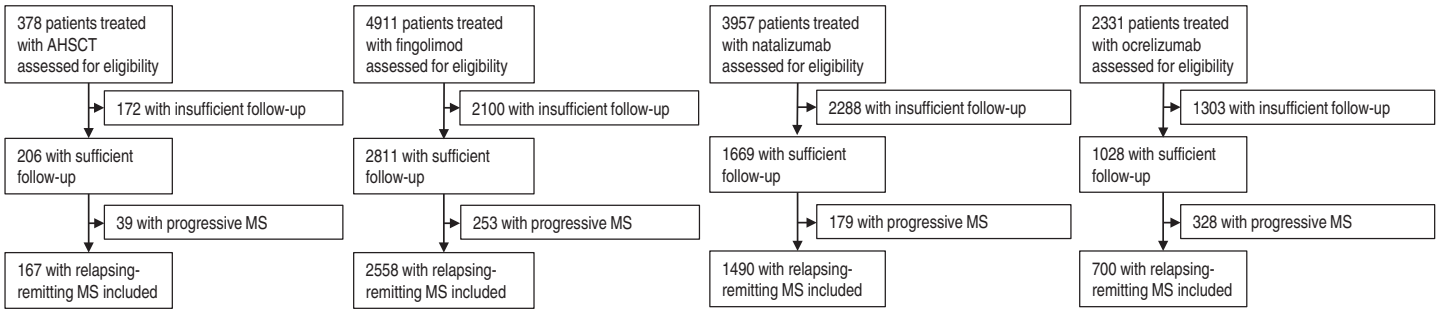
Table 1

Characteristics of the matched patient groups at baseline

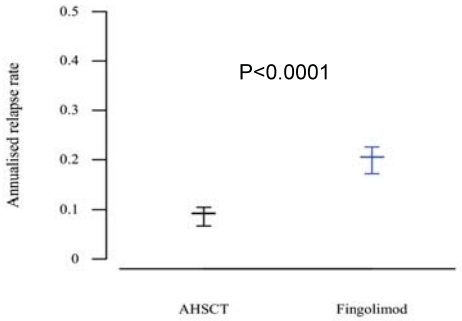
	AHSCT	fingolimod	d	AHSCT	natalizumab	d	AHSCT	ocrelizumab	d
patients matched	144	769		146	730		110	343	
sex, M (%)	44 (30.6)	224 (29.1)	0.03	45 (30.8)	224 (30.6)	0.01	36 (32.7)	120 (35.0)	0.05
age (mean (SD))	35.7 (8.7)	35.3 (9.4)	0.04	35.5 (8.7)	36.0 (9.0)	0.06	37.0 (8.6)	37.1 (10.6)	0.01
MS duration, y (mean (SD))	8.12 (5.58)	8.17 (6.07)	0.01	7.92 (5.63)	8.17 (6.22)	0.04	8.68 (5.42)	8.48 (7.34)	0.03
relapses in prior 12 months (mean (SD))	0.80 (0.97)	0.81 (0.92)	0.02	0.82 (1.01)	0.86 (0.89)	0.04	0.79 (0.95)	0.77 (0.94)	0.03
relapses in prior 24 months (mean (SD))	1.12 (1.27)	1.17 (1.20)	0.04	1.17 (1.33)	1.19 (1.14)	0.02	1.15 (1.25)	1.08 (1.19)	0.06
baseline EDSS (mean (SD))	3.74 (1.63)	3.75 (1.82)	0.00	3.86 (1.66)	3.88 (1.92)	0.02	3.50 (1.60)	3.58 (1.87)	0.05
patients with pre-baseline progression (%)	23 (16.0)	168 (21.8)	0.15	23 (15.8)	197(27.0)	0.28	20 (18.2)	69 (20.0)	0.05
top pre-baseline DMT (%)			0.05			0.03			0.03
low-efficacy	18 (12.5)	104 (13.5)		18 (12.3)	87 (12.0)		14 (12.7)	43 (12.5)	
medium-efficacy	9 (6.2)	46 (5.9)		12 (8.2)	55 (7.5)		10 (9.1)	30 (8.7)	
high-efficacy	24 (16.7)	139 (18.2)		17 (11.6)	88 (12.1)		22 (20.0)	73 (21.3)	
unknown	93 (64.6)	480 (62.4)		99 (67.8)	500 (68.5)		64 (58.2)	197 (57.5)	
region (%)			0.03			0.07			0.05
Asia-Pacific	46 (31.9)	236 (30.7)		46 (31.5)	230 (31.5)		45 (40.9)	148 (43.2)	
Europe	73 (50.7)	392 (51.0)		73 (50.0)	346 (47.4)		50 (45.5)	148 (43.0)	
North America	25 (17.4)	141 (18.3)		27 (18.5)	154 (21.1)		15 (13.6)	47 (13.8)	
study follow-up, y (mean (SD))	4.01 (2.59)	2.84 (2.43)	0.46	4.08 (2.67)	2.51 (2.22)	0.64	3.78 (2.43)	1.52 (0.94)	1.22
year of baseline (median [IQR])	2015 [2013, 2017]	2013 [2012, 2015]	0.17	2015 [2013, 2016]	2012 [2010, 2015]	0.44	2016 [2014, 2017]	2018 [2018, 2019]	1.40
MRI: T2 lesion number (%)			0.76			0.84			1.04
0	0. (0.0)	4 (0.5)		0 (0.0)	1 (0.1)		0 (0.0)	9 (2.5)	
1-2	3 (2.1)	27 (3.5)		3 (2.1)	35 (4.8)		3 (2.7)	9 (2.7)	
3-8	5 (3.5)	130 (17.0)		4 (2.7)	125 (17.2)		5 (4.5)	53 (15.6)	

9+	45 (31.2)	374 (48.6)		46 (31.5)	367 (50.3)		38 (34.5)	220 (64.1)		
unknown	91 (63.2)	234 (30.5)		93 (63.7)	202 (27.7)		64 (58.2)	52 (15.1)		
visit interval, months (mean (SD))	8.38 (4.43)	4.46 (4.02)	0.93	8.39 (4.42)	3.99 (4.41)	0.99	8.77 (4.70)	5.48 (3.57)	0.79	

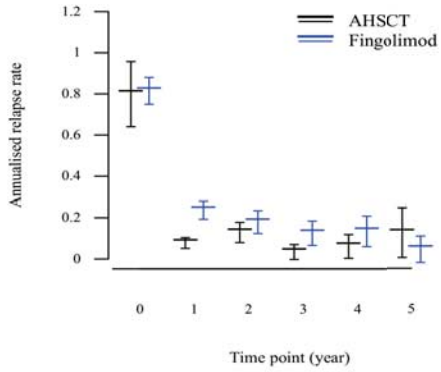
The patient characteristics are presented for each pair of matched treatment groups separately.
d, standardised difference (Cohen's d); SD, standard deviation; EDSS, Expanded Disability Status Scale; IQR, interquartile range


378 patients treated with AHSCT assessed for eligibility
172 with insufficient follow-up
206 with sufficient follow-up
39 with progressive MS
167 with relapsing-remitting MS included
4911 patients treated with fingolimod assessed for eligibility
2100 with insufficient follow-up
2811 with sufficient follow-up
253 with progressive MS
2558 with relapsing-remitting MS included
3957 patients treated with natalizumab assessed for eligibility
2288 with insufficient follow-up
1669 with sufficient follow-up
179 with progressive MS
1490 with relapsing-remitting MS included
2331 patients treated with ocrelizumab assessed for eligibility
1303 with insufficient follow-up
1028 with sufficient follow-up
328 with progressive MS
700 with relapsing-remitting MS included

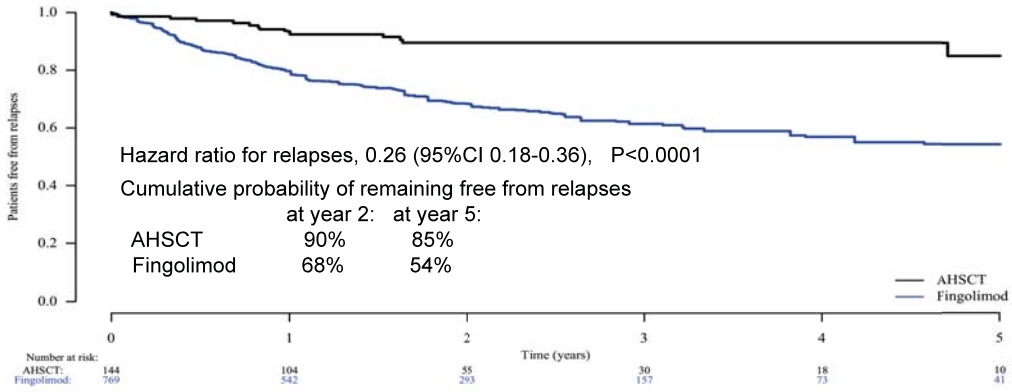
A Overall annualised relapse rate



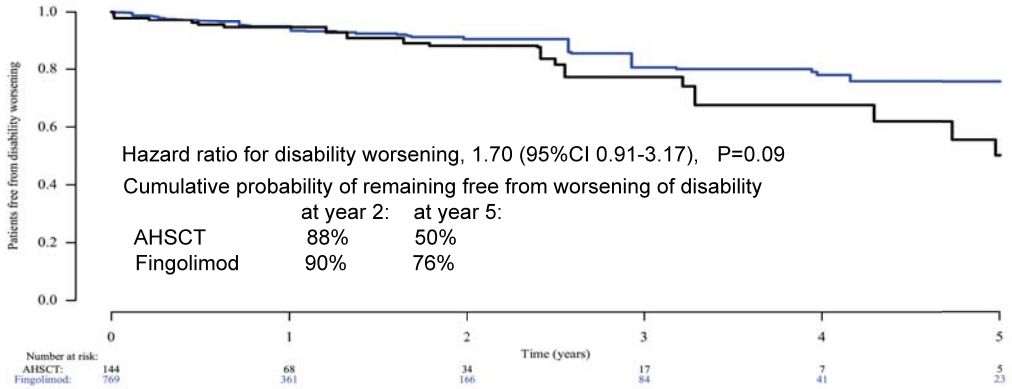
B Annual relapse rate by year



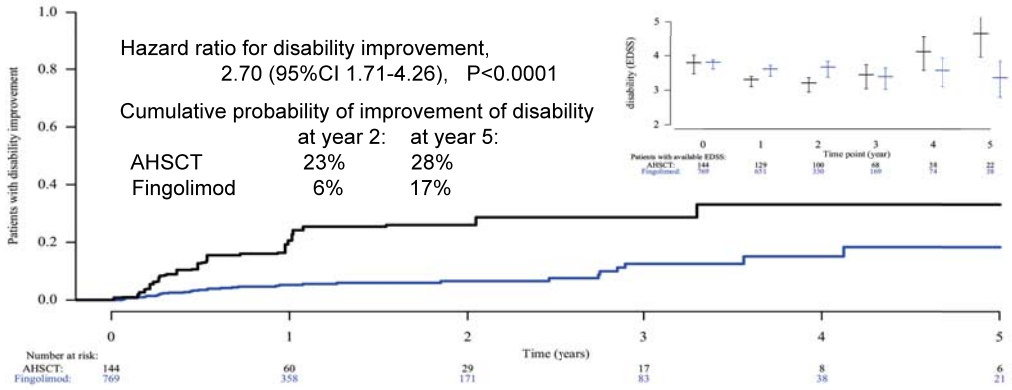
C Freedom from relapses



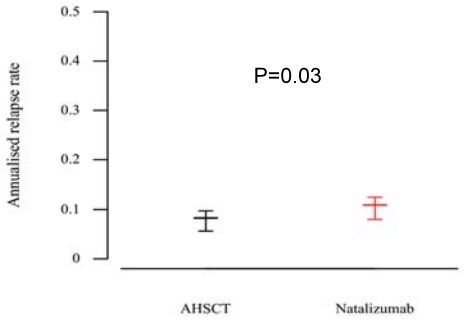
D Confirmed disability worsening



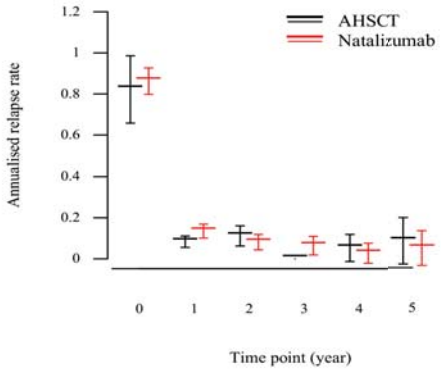
E Confirmed disability improvement



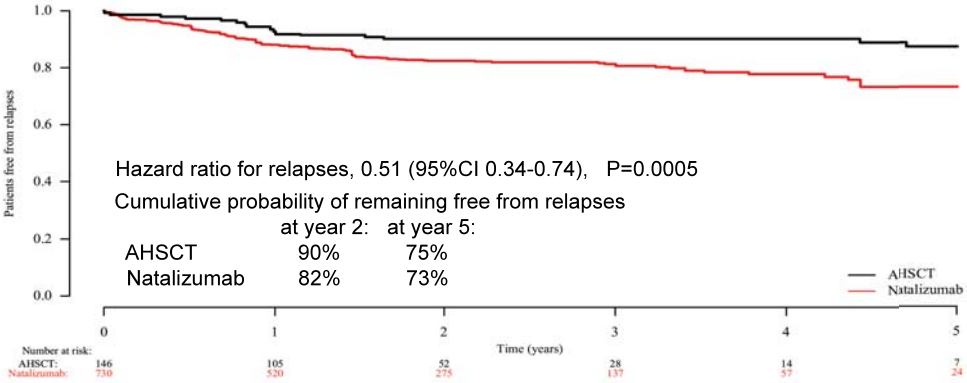
A Overall annualised relapse rate



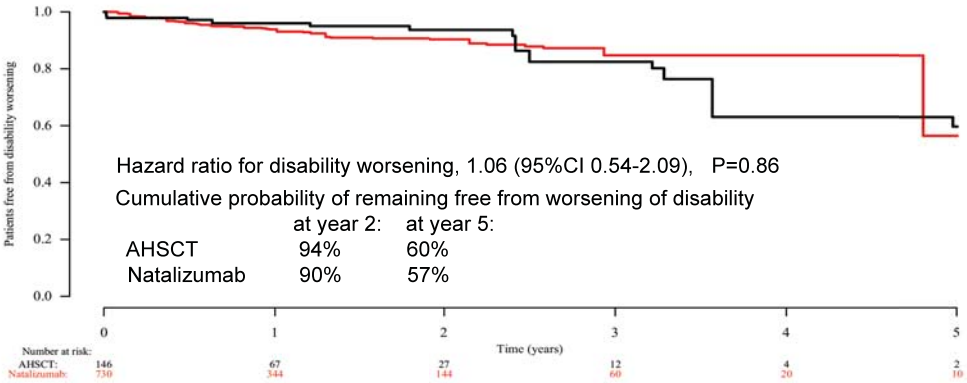
B Annual relapse rate by year



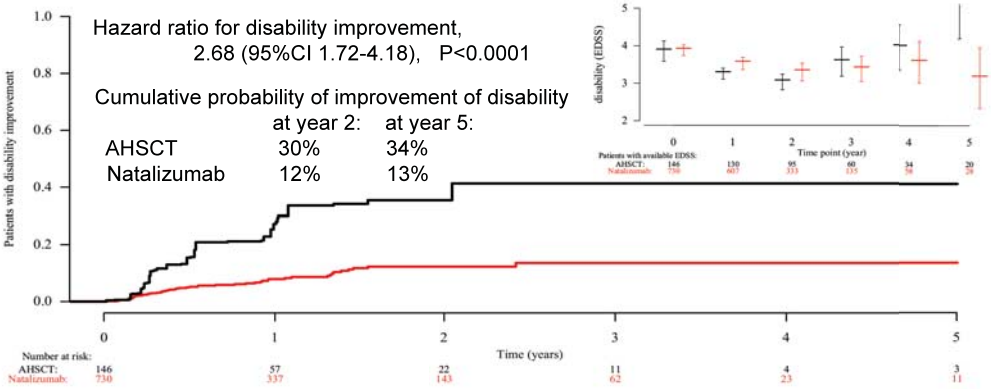
C Freedom from relapses

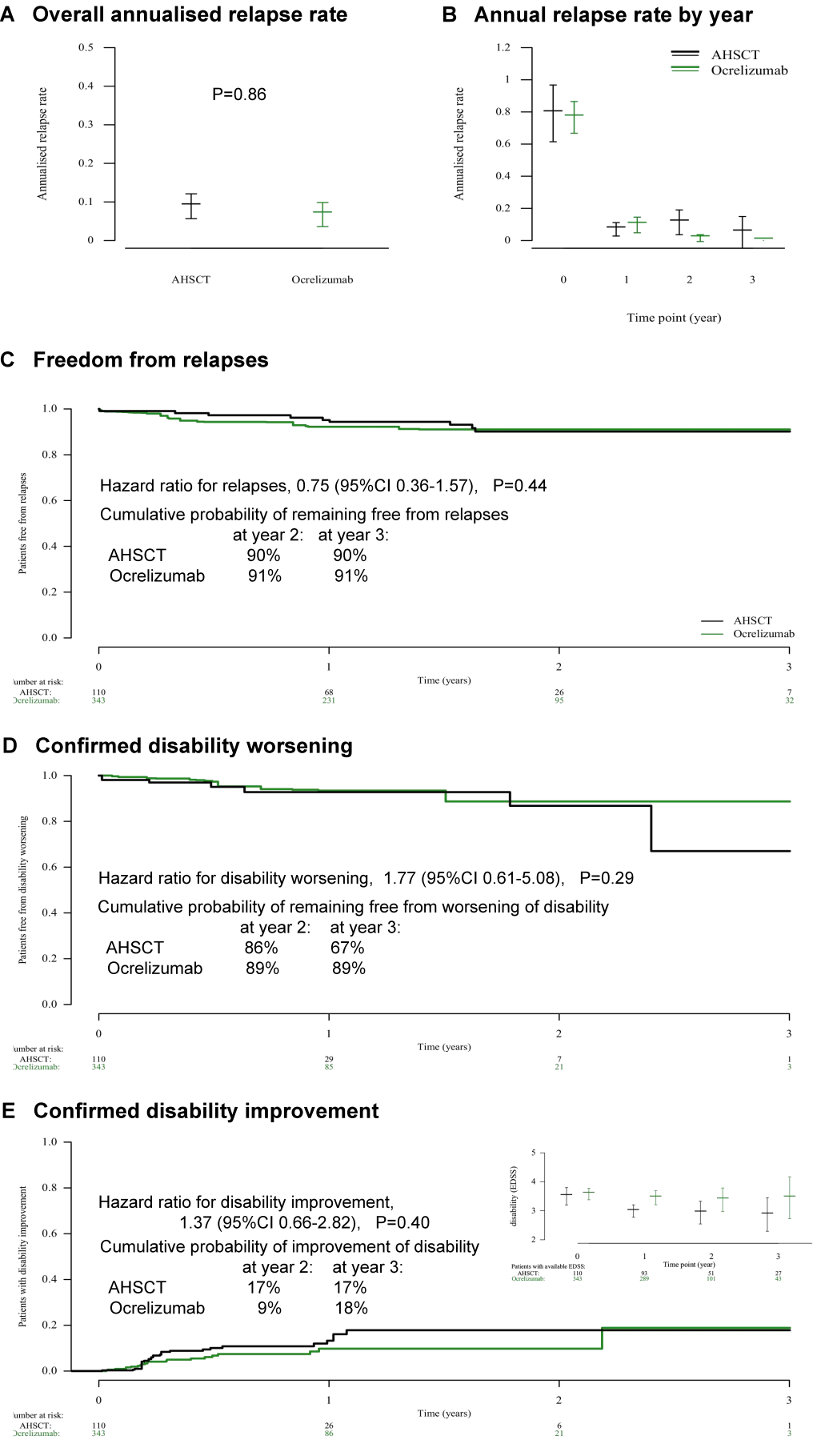


D Confirmed disability worsening



E Confirmed disability improvement




A Overall annualised relapse rate
Annualised relapse rate
0.5
0.4
0.3
0.2
0.1
0
P=0.86
AHSCT
Ocrelizumab
B Annual relapse rate by year
Annualised relapse rate
1.2
1
0.8
0.6
0.4
0.2
0
AHSCT
Ocrelizumab
0
1
2
3
Time point (year)
C Freedom from relapses
Patients free from relapses
1.0
0.8
0.6
0.4
0.2
0.0
Hazard ratio for relapses, 0.75 (95%CI 0.36-1.57), P=0.44
Cumulative probability of remaining free from relapses
at year 2: at year 3:
AHSCT 90% 90%
Ocrelizumab 91% 91%
AHSCT
Ocrelizumab
0
1
2
3
Time (years)
umber at risk:
AHSCT: 110 68 26 7
Ocrelizumab: 343 231 95 32
D Confirmed disability worsening
Patients free from disability worsening
1.0
0.8
0.6
0.4
0.2
0.0
Hazard ratio for disability worsening, 1.77 (95%CI 0.61-5.08), P=0.29
Cumulative probability of remaining free from worsening of disability
at year 2: at year 3:
AHSCT 86% 67%
Ocrelizumab 89% 89%
0
1
2
3
Time (years)
umber at risk:
AHSCT: 110 29 7 1
Ocrelizumab: 343 85 21 3
E Confirmed disability improvement
Patients with disability improvement
1.0
0.8
0.6
0.4
0.2
0.0
Hazard ratio for disability improvement,
1.37 (95%CI 0.66-2.82), P=0.40
Cumulative probability of improvement of disability
at year 2: at year 3:
AHSCT 17% 17%
Ocrelizumab 9% 18%
disability (EDSS)
5
4
3
2
0
1
2
3
Time point (year)
Patients with available EDSS:
AHSCT: 110 93 51 27
Ocrelizumab: 343 289 101 43
0
1
2
3
Time (years)
umber at risk:
AHSCT: 110 26 6 1
Ocrelizumab: 343 86 21 3