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Comparative Effectiveness of Autologous Hematopoietic Stem Cell Transplant vs Fingolimod, Natalizumab, and Ocrelizumab in Highly Active Relapsing-Remitting Multiple Sclerosis

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5
6 **Authors (limited to 50 authors):**

7 Tomas Kalincik, MD, PhD^{1,2}; Sifat Sharmin, PhD^{1,2}; Izanne Roos, MBChB, PhD^{1,2}; Mark S.
8 Freedman, MD³; Harold Atkins, MD⁴; Joachim Burman, MD, PhD⁵; Jennifer Massey, MBBS,
9 PhD^{6,7}; Ian Sutton, MBBS, PhD^{6,8}; Barbara Withers, MD, PhD^{9,7}; Richard Macdonell, MD,
10 PhD^{10,11}; Andrew Grigg, MD, PhD^{12,11}; Øivind Torkildsen, MD, PhD¹³; Lars Bo, MD, PhD¹³;
11 Anne Kristine Lehmann, MD, PhD¹⁴; Eva Kubala Havrdova, MD, PhD¹⁵; Eva Krasulova, MD,
12 PhD¹⁵; Marek Trneny, MD, PhD¹⁶; Tomas Kozak, MD, PhD¹⁷; Anneke van der Walt, MBBS,
13 PhD^{18,19}; Helmut Butzkueven, MBBS, PhD^{18,19}; Pamela McCombe, MBBS^{20,21}; Olga Skibina,
14 MBBS^{22,23,18}; Jeannette Lechner-Scott, MD, PhD^{24,25}; Barbara Willekens, MD, PhD^{26,27};
15 Elisabetta Cartechini, MD²⁸; Serkan Ozakbas, MD²⁹; Raed Alroughani, MD³⁰; Jens Kuhle,
16 MD, PhD³¹; Francesco Patti, MD^{32,33}; Pierre Duquette, MD³⁴; Alessandra Lugaresi, MD,
17 PhD^{35,36}; Samia J. Khoury, MD, PhD³⁷; Mark Slee, MD, PhD³⁸; Recai Turkoglu, MD³⁹;
18 Suzanne Hodgkinson, MD⁴⁰; Nevin John, MD, PhD^{41,42}; Davide Maimone, MD⁴³; Maria Jose
19 Sa, MD⁴⁴; Vincent van Pesch, MD, PhD^{45,46}; Oliver Gerlach, MD, PhD^{47,48}; Guy Laureys,
20 MD⁴⁹; Liesbeth Van Hijfte, MD⁴⁹; Rana Karabudak, MD⁵⁰; Daniele Spitaleri, MD⁵¹; Tunde
21 Csepány, MD, PhD⁵²; Riadh Gouider, MD^{53,54}; Tamara Castillo-Triviño, MD⁵⁵; Bruce Taylor,
22 MD, PhD^{64,65};
23 Basil Sharrack, MD, PhD⁵⁶; John A Snowden, MD, PhD⁵⁷
24 on behalf of the MSBase authors and MSBase collaborators.

25
26 **MSBase authors to be listed under the group authorship:**

27 Saloua Mrabet, MD^{53,54}; Justin Garber, MBBS⁵⁸; Jose Luis Sanchez-Menoyo, MD⁵⁹; Eduardo
28 Aguera-Morales, MD⁶⁰; Yolanda Blanco, MD⁶¹; Abdullah Al-Asmi, MD⁶²; Bianca Weinstock-
29 Guttman, MD⁶³; Yara Fragoso, MD⁶⁶; Koen de Gans, MD⁶⁷; Allan Kermodé, MD, PhD^{68,69}

30
31
32
33 **Affiliations:**

34 1, Neuroimmunology Centre, Department of Neurology, Royal Melbourne Hospital,
35 Melbourne, Australia
36 2, CORE, Department of Medicine, University of Melbourne, Melbourne, Australia
37 3, University of Ottawa, Department of Medicine, Ottawa Hospital Research Institute, Ottawa,
38 Canada
39 4, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Canada
40 5. Department of Medical Sciences, Neurology, Uppsala University, Uppsala, Sweden
41 6. Department of Neurology, St Vincent's Hospital Sydney, Sydney, Australia
42 7. St Vincent's Clinical School, University of New South Wales, Sydney, Australia
43 8. University of Sydney, Sydney, Australia
44 9. Department of Haematology, St Vincent's Hospital Sydney, Sydney, Australia
45 10. Department of Neurology, Austin Health, Melbourne, Australia
46 11. University of Melbourne, Melbourne, Australia
47 12. Department of Haematology, Austin Health, Melbourne, Australia
48 13. Department of Neurology, Haukeland University Hospital, Bergen, Norway
49 14. Department of Haematology, Haukeland University Hospital, Bergen, Norway
50 15. Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine,
51 Charles University in Prague and General University Hospital, Prague, Czech Republic
52 16. Department of Haematology, First Faculty of Medicine, Charles University in Prague and
53 General University Hospital, Prague, Czech Republic

- 54 17. Department of Haematology, 3rd Faculty of Medicine, Charles University in Prague, and
- 55 University Hospital Kralovske Vinohrady, Prague, Czech Republic
- 56 18. Department of Neurology, The Alfred Hospital, Melbourne, Australia
- 57 19. Central Clinical School, Monash University, Melbourne, Australia
- 58 20. University of Queensland, Brisbane, Australia
- 59 21. Royal Brisbane and Women's Hospital, Brisbane, Australia
- 60 22. Department of Neurology, Box Hill Hospital, Melbourne, Australia
- 61 23. Monash University, Melbourne, Australia
- 62 24. School of Medicine and Public Health, University Newcastle, Newcastle, Australia
- 63 25. Department of Neurology, John Hunter Hospital, Hunter New England Health, Newcastle,
- 64 Australia
- 65 26. Department of Neurology, Antwerp University Hospital, Edegem, Belgium
- 66 27. Translational Neurosciences Research Group, Faculty of Medicine and Health Sciences,
- 67 University of Antwerp, Wilrijk, Belgium
- 68 28. UOC Neurologia, Azienda Sanitaria Unica Regionale Marche - AV3, Macerata, Italy
- 69 29. Dokuz Eylul University, Konak/Izmir, Turkey
- 70 30. Division of Neurology, Department of Medicine, Amiri Hospital, Sharq, Kuwait
- 71 31. Neurologic Clinic and Policlinic, Departments of Medicine and Clinical Research,
- 72 University Hospital and University of Basel, Basel, Switzerland
- 73 32. Department of Medical and Surgical Sciences and Advanced Technologies, GF
- 74 Ingrassia, Catania, Italy
- 75 33. Multiple Sclerosis Center, University of Catania, Catania, Italy
- 76 34. CHUM MS Center and Universite de Montreal, Montreal, Canada
- 77 35. IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
- 78 36. Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, Bologna,
- 79 Italy
- 80 37. Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut
- 81 Medical Center, Beirut, Lebanon
- 82 38. Flinders University, Adelaide, Australia
- 83 39. Haydarpasa Numune Training and Research Hospital, Istanbul, Turkey
- 84 40. Liverpool Hospital, Sydney, Australia
- 85 41, Monash Medical Centre, Melbourne, Australia
- 86 42. Department of Medicine, School of Clinical Sciences, Monash University, Melbourne,
- 87 Australia
- 88 43. Garibaldi Hospital, Catania, Italy
- 89 44. Department of Neurology, Centro Hospitalar Universitario de Sao Joao, Porto, Portugal
- 90 45. Cliniques Universitaires Saint-Luc, Brussels, Belgium
- 91 46. Université Catholique de Louvain
- 92 47. Academic MS Center Zuyderland, Department of Neurology, Zuyderland Medical Center,
- 93 Sittard-Geleen, The Netherlands
- 94 48. School for Mental Health and Neuroscience, Maastricht University, Maastricht, The
- 95 Netherlands
- 96 49. Department of Neurology, University Hospital Ghent, Ghent, Belgium
- 97 50. Department of Neurology, Hacettepe University Hospitals, Ankara, Turkey
- 98 51. Azienda Ospedaliera di Rilievo Nazionale San Giuseppe Moscati Avellino, Avellino, Italy
- 99 52. Department of Neurology, Faculty of Medicine, University of Debrecen, Debrecen,
- 100 Hungary
- 101 53. Department of Neurology, Razi University Hospital, Manouba, Tunis, Tunisia
- 102 54. Faculty of Medicine of Tunis, University of Tunis El Manar, Tunis, Tunisia
- 103 55. Hospital Universitario Donostia, San Sebastián, Spain
- 104 56. Department of Neurology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield,
- 105 UK
- 106 57. Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust,
- 107 Sheffield, UK
- 108 58. Westmead Hospital, Sydney, Australia
- 109 59. Hospital de Galdakao-Usansolo, Galdakao, Spain

- 110 60. University Hospital Reina Sofia, Cordoba, Spain
111 61. Center of Neuroimmunology, Service of Neurology, Hospital Clinic de Barcelona,
112 Barcelona, Spain
113 62. Department of Medicine, Sultan Qaboos University Hospital, Al-Khodh, Oman
114 63. Department of Neurology, Buffalo General Medical Center, Buffalo, United States
115 64. Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
116 65. Royal Hobart Hospital, Hobart, Australia
117 66. Universidade Metropolitana de Santos, Santos, Brazil
118 67. Groene Hart Ziekenhuis, Gouda, Netherlands
119 68. Perron Institute, University of Western Australia, Nedlands, Australia
120 69. Institute of Immunology and Infectious Diseases, Murdoch University, Perth, Australia; Sir
121 Charles Gairdner Hospital
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136

137 **Corresponding author**

138 Tomas Kalincik; L4 East, CORe, Royal Melbourne Hospital, 300 Grattan St, Parkville
139 VIC 3050, Australia; Tel: +61 3 9342 4404, Fax: +61 3 9349 5997; email:
140 tomas.kalincik@unimelb.edu.au
141
142
143
144

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156
157 **Keywords**

158 stem cells, disease modifying therapy, relapses, disability, propensity score
159

160 **KEY POINTS**

161 **Question**

162 The evidence regarding the effectiveness of autologous haematopoietic stem cell
163 transplantation (AHSCT) is limited. We have conducted a literature search using the PubMed
164 database, with search terms “haematopoietic stem cell transplantation” AND “relapsing-
165 remitting multiple sclerosis” AND “disease modifying therapy” AND “trial” published between
166 1/1/1990 and 1/10/2022 in any language. Only two randomised clinical trials were identified.
167 In one trial, AHSCT used in 9 patients with relapsing or progressive multiple sclerosis was
168 superior to mitoxantrone in reducing clinical or radiological episodic inflammatory activity. In
169 another trial, AHSCT used in 55 patients with relapsing-remitting multiple sclerosis was
170 superior to a mixed group of various therapies in controlling relapses and disability.
171 Presently, information about the effectiveness of AHSCT in comparison to individual most
172 potent disease modifying therapies for relapsing-remitting multiple sclerosis, such as
173 natalizumab or ocrelizumab, is lacking.

174

175 **Findings**

176 This observational study, utilising a composite cohort from specialised MS centres and the
177 MSBase international registry, compares the effectiveness of AHSCT to one medium-efficacy
178 and two high-efficacy disease modifying therapies – fingolimod, natalizumab and
179 ocrelizumab – in patients with relapsing-remitting multiple sclerosis, high frequency of
180 relapses and moderate disability. While the included patients treated with AHSCT tended to
181 be younger, with shorter disease duration and with greater disability, the matching procedure
182 has closely aligned the compared groups on all matched characteristics. It shows that
183 AHSCT is substantially superior to fingolimod and marginally superior to natalizumab in
184 preventing relapses over 5 years. AHSCT is also associated with a higher rate of recovery
185 from disability in comparison to fingolimod and natalizumab. With a shorter follow-up of 3
186 years, the study found no evidence of difference in clinical outcomes between AHSCT and

187 ocrelizumab. Complications of AHSCT are common. One treatment-related death was
188 reported among the 159 AHSCT-treated patients with relapsing remitting MS.

189

190 **Meaning**

191 The results of the present study indicate that in relapsing-remitting multiple sclerosis, the
192 clinical effectiveness of AHSCT is considerably superior to fingolimod and marginally
193 superior to natalizumab. The study did not find evidence for its clinical superiority over
194 ocrelizumab over a shorter follow-up period within a less powered cohort.

195 **ABSTRACT**

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

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

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

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

205 **Participants:** The study included 4915 patients with relapsing-remitting MS treated with
206 AHSCT, fingolimod, natalizumab or ocrelizumab, with ≥ 2 -year on-treatment follow-up
207 including ≥ 2 disability assessments. 7918 patients did not fulfil the inclusion criteria and were
208 excluded. The patients were matched on a propensity score derived from their clinical and
209 demographic characteristics.

210 **Exposure:** AHSCT or fingolimod, natalizumab, ocrelizumab.

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

214 **Results:** While the pre-match AHSCT cohort (n=167) was younger and with greater disability
215 than the fingolimod (n=2558), natalizumab (n=1490) and ocrelizumab (n=700) cohorts, the
216 matched groups were closely aligned. They were 65-70% women, of mean age 35-37, mean
217 disease duration of 8-9 years, average EDSS 3.5-4 and high frequency of relapses (mean
218 0.77-0.86) in the preceding year. In comparison to fingolimod (n=769), AHSCT (n=144) was
219 associated with fewer relapses (ARR: mean \pm SD 0.09 \pm 0.30 vs. 0.20 \pm 0.44), similar risk of
220 EDSS worsening (HR=1.70, 95%CI=0.91-3.17) and higher chance of disability improvement
221 (HR=2.70, 95%CI=1.71-4.26) over 5 years. Compared to natalizumab (n=730), AHSCT
222 (n=146) was associated with marginally lower ARR (0.08 \pm 0.31 vs. 0.10 \pm 0.34), similar risk of

223 EDSS worsening (HR=1.06, 95%CI=0.54-2.09), and higher chance of EDSS improvement
224 (HR=2.68, 95%CI=1.72-4.18) over 5 years. AHSCT (n=110) and ocrelizumab (n=343) were
225 associated with similar ARR (0.09±0.34 vs. 0.06±0.32), EDSS worsening (HR=1.77,
226 95%CI=0.61-5.08) and EDSS improvement (HR=1.37, 95%CI=0.66-2.82) over 3 years.
227 AHSCT-related mortality occurred in 1 of 159 patients (0.6%).

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

232

233 **TEXT**

234 **INTRODUCTION**

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

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

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

257

258

259 **METHODS**

260 **Patients and data**

261 Data, recorded between 2006-2021, were obtained from 6 cohorts treated with AHST at
262 specialised centres (in Ottawa, Uppsala, Sheffield, Bergen, Sydney and Melbourne) and 94
263 centres in 27 countries from the MSBase registry (WHO study registration
264 ACTRN12605000455662). The study was approved by the Melbourne Health Human
265 Research Ethics Committee and the site institutional review boards. Patients provided written
266 informed consent, as required. The data are the property of the individual centres; they can
267 be requested for replication of this study, at the discretion of each principal investigator. This
268 study is reported following the STROBE guideline.

269 The inclusion criteria were definite relapsing-remitting MS,²⁰⁻²² first exposure to one of the
270 study therapies, no exposure to alemtuzumab or participation in randomised clinical trials
271 within the prior 10 years, minimum recorded follow-up 2 months prior to treatment start and 2
272 post-baseline disability scores (including ≥ 1 on treatment), persistence on study therapy for
273 ≥ 1 month and minimum dataset (consisting of sex, age, date of first MS symptom, dates of
274 clinical relapses, clinical MS course, disability score at treatment commencement (-9 months
275 to +1 month)). All consecutive patients treated with AHST were included.

276

277 **Procedures**

278 Patients received AHST following protocols specific to the treating centres.^{2,3,5,23}
279 Autologous haematopoietic stem cells were mobilised using cyclophosphamide 2-4.5 g/m² IV
280 with granulocyte colony stimulating factor 5-10 μ g/kg. In a small number of patients, the
281 mobilisation used granulocyte colony stimulating factor only or in combination with
282 methylprednisolone. The cells were then harvested by leukapheresis and cryopreserved. In
283 approximately one third of patients, the graft was depleted of mature immune cells with CD34
284 immunomagnetic selection. The transplant conditioning regimens were commenced >3
285 weeks after mobilisation and included BEAM (carmustine 300mg/m², etoposide 200-
286 800mg/m², cytarabine 200mg/m² and melphalan 140mg/m²), busulfan with
287 cyclophosphamide 50mg/kg, or cyclophosphamide 200mg with anti-thymocyte globulin

288 10mg/kg. Rabbit/horse anti-thymocyte globulin was used in 84% of patients. Infection
289 prophylaxis was used as per local protocols.

290 The patients included in the DMT arms were treated either with fingolimod (0.5mg oral daily),
291 ocrelizumab (600mg IV every 6 months) or natalizumab (300µg IV every 4 weeks). Baseline
292 was defined as the first day of AHSCT conditioning or commencement of the DMT. Patients
293 were censored at discontinuing therapy (with the minimum duration of treatment effect set at
294 60 days after starting fingolimod or natalizumab, 6 months after ocrelizumab, and 5 years
295 after AHSCT),²⁴ commencing another DMT, or at the last recorded disability score, whichever
296 occurred first.

297 The analysed data were recorded as part of routine practice, mostly at tertiary MS services,
298 with real-time data entry. The MSBase Study Protocol stipulates minimum annual acquisition
299 of disability scores, but patients with less frequent visits were not excluded.²⁵ Data from
300 different sources were mapped, combined and underwent a rigorous quality procedure
301 (eTable 1).²⁶

302

303 **Outcomes**

304 The primary endpoint was the on-treatment annualised relapse rate (ARR). A relapse was
305 defined as new symptoms or exacerbation of existing symptoms persisting for ≥24 hours, in
306 the absence of concurrent illness/fever, and occurring ≥30 days after a previous relapse.²⁷

307 Confirmation of relapses by Expanded Disability Status Scale (EDSS) was not mandated.

308 Individual ARR between baseline and censoring was calculated.

309 Secondary endpoints were the cumulative hazards of first post-baseline relapse, the
310 proportions of patients free from disability worsening and with disability improvement.

311 Disability was scored by EDSS scorers (Neurostatus certification was required at each site),
312 excluding scores recorded ≤30 days of a prior relapse. Disability worsening was defined as

313 an increase in EDSS by 1 step (1.5 steps if baseline EDSS=0, and 0.5 steps if baseline
314 EDSS>5.5) confirmed by subsequent EDSS scores over ≥6 months. Disability improvement

315 was defined as a decrease in EDSS by 1 step (1.5 step if baseline EDSS=1.5 and 0.5 steps
316 if baseline EDSS>6) confirmed by subsequent EDSS scores over ≥ 6 months.²⁸

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

320

321 **Statistical analysis**

322 This study emulated three clinical trials comparing AHSCT with fingolimod, natalizumab and
323 ocrelizumab (eTable 2).²⁹ Matching and statistical analyses were conducted using R
324 (v4.1.1).³⁰ Individual patients were matched on their propensity of receiving either of the
325 compared therapies in 1:10 variable matching ratio without replacement within a caliper of
326 0.1 standard deviations of the propensity score. Individual propensity scores were calculated
327 using a multivariable logistic model of treatment allocation that utilised demographic and
328 clinical variables available at baseline as independent variables: sex, age, EDSS, number of
329 relapses 12 and 24 months before baseline, time from first symptom of MS to baseline, the
330 most effective prior DMT and geographical region.

331 All subsequent analyses were designed as paired models with weighting to account for the
332 variable matching ratio (cumulative weight per patient ≤ 1). The pairwise-censored on-
333 treatment follow-up was determined in each matched pair as the shorter of the two patient
334 follow-up periods, to mitigate attrition bias, informative censoring and the effect of differential
335 treatment persistence.¹²

336 ARR_s were compared with a weighted negative binomial model with cluster effect for
337 matched pairs. The cumulative hazards of first relapse, disability worsening and disability
338 improvement were evaluated with weighted conditional proportional hazards models (Cox)
339 adjusted for visit frequency and with robust estimation of variance. Interaction term for
340 treatment and time was introduced in the models where Schoenfeld's global test indicated
341 violation of the proportionality of hazards assumption.

342 Robustness of the statistically significant differences to unidentified confounders was
343 quantified with Hodges-Lehmann τ .³¹ Where no evidence of difference between the
344 compared groups was found, the minimum detectable effect at $\alpha=0.05$ and $1-\beta=0.80$ was
345 estimated with 200 simulations per treatment pair and outcome.

346

347

348 **RESULTS**

349 A total of 167 (AHSCT), 2558 (fingolimod), 1490 (natalizumab), and 700 (ocrelizumab)
350 patients fulfilling the inclusion criteria were identified (Figure 1, eTable 3). Among the AHSCT
351 cohort, the conditioning intensity was used as follows: high-intensity in 43 patients (26%),
352 intermediate-intensity myeloablative in 49 patients (29%), intermediate-intensity
353 lymphoablative in 64 patients (38%) and low- to intermediate-intensity in 11 patients (7%).¹⁹
354 As expected, the four unmatched groups differed in their baseline characteristics (eTable 4).
355 From the logistic models used to derive the propensity scores, it is apparent that patients
356 tended to commence AHSCT at younger age, higher disability, and shorter disease duration
357 compared to the three studied DMTs (eTable 5).

358

359 **Effectiveness**

360 The numbers of patients retained in the three pairwise matched comparisons are shown in
361 Table 1. The matching procedure significantly decreased the differences in propensity scores
362 between the compared groups from 0.35-0.41 to 0.002-0.005, corresponding to a 99.0-
363 99.5% improvement in the overall balance. The close match on individual characteristics is
364 demonstrated in Table 1 (standardised differences $\leq 10\%$ for all matched characteristics). As
365 a result of pairwise censoring, on-treatment follow-up was identical in the matched groups.
366 The groups were not matched on the between-visit intervals, for which the analyses were
367 then adjusted.

368 Patients treated with AHSCT experienced fewer relapses than those treated with fingolimod
369 (Figure 2; ARR, mean \pm standard deviation [SD] 0.09 ± 0.30 vs. 0.20 ± 0.44 , respectively,

370 $p < 0.0001$). This observation was robust to unmeasured confounding ($\Gamma > 100\%$) and
371 confirmed by the cumulative hazard of relapse (hazard ratio [HR]=0.26, 95% confidence
372 interval [95%CI]=0.18-0.36). We did not find evidence for difference in the cumulative
373 hazards of 6-month confirmed disability worsening over up to 5 years (HR=1.70,
374 95%CI=0.91-3.17). AHSCT was superior in facilitating 6-month confirmed improvement of
375 disability than fingolimod (HR=2.70; 95%CI=1.71-4.26).

376 The ARR in the AHSCT group was marginally lower than in the natalizumab group (Figure 3;
377 0.08 ± 0.31 vs. 0.10 ± 0.34 , respectively, $p = 0.03$), as also confirmed by the cumulative hazard
378 of relapses (HR=0.51, 95%CI=0.34-0.74). This observation was moderately robust to
379 unmeasured confounding ($\Gamma = 20\%$). The study did not find evidence for difference in the 6-
380 month confirmed disability worsening between AHSCT and natalizumab (HR=1.06,
381 95%CI=0.54-2.09), with similar proportions of patients who experienced disability worsening
382 by years 2 and 5. AHSCT was superior in facilitating 6-month confirmed improvement of
383 disability consistently during the 5-year follow-up (HR=2.68; 95%CI=1.72-4.18).

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

392 According to the power analysis, the emulated trials were sufficiently powered to detect
393 minimum differences of 0.17 relapses per year and 19-69% of the cumulative hazards of
394 outcome events (eTable 6).

395

396 **Safety**

397 Safety data were available for the patients treated with AHSCT. Among the 159 patients who
398 were matched in at least one of the pairwise analyses, 37 patients experienced febrile
399 neutropenia during mobilisation, 18 patients experienced serum sickness, and 14 patients
400 required ICU admission. 82 serious adverse events were recorded in 58 patients after
401 discharge post-AHSCT, these consisted mainly of infections (49), especially of viral aetiology
402 (34; eTable 7). Treatment-related death was reported in one patient (0.6%, due to veno-
403 occlusive disease of the liver post-busulfan).

404

405

406 **DISCUSSION**

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

420 To date, only two randomised controlled trials of AHSCT have been completed. A phase 2
421 trial compared a mixed group of 9 patients with relapsing or progressive MS treated with
422 myeloablative AHSCT with 12 patients treated with mitoxantrone. The trial concluded that
423 AHSCT was more effective than mitoxantrone in reducing clinical and radiological episodic
424 inflammatory activity.³³ The phase 3 MIST trial compared 55 patients with relapsing-remitting

425 MS randomised to non-myeloablative AHSC with the same number randomised to
426 escalation of DMT.⁷ The trial reported superiority of AHSC in reducing the risk of disability
427 worsening, relapses and MRI activity. Because the interventions in the DMT escalation group
428 ranged from interferon β to natalizumab with or without add-on methylprednisolone,
429 rituximab, plasmapheresis, cyclophosphamide or intravenous immunoglobulins, the study did
430 not generate evidence regarding the effectiveness of AHSC head-to-head with the most
431 potent available DMTs.

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

443 Our present study enables us to draw conclusions separately about the effectiveness of
444 AHSC vs. two high-efficacy and one medium-efficacy DMT among patients with highly
445 active relapsing-remitting MS. The cohort represents typical clinical scenarios in which
446 AHSC is presently considered – highly inflammatory disease in young patients with prior
447 failures of potent DMTs and mild-moderate disability. With the comparison of AHSC against
448 fingolimod we have established discriminative ability of the matched analysis, clearly
449 demonstrating the expected superiority of AHSC. In comparison to natalizumab, AHSC
450 was marginally superior at reducing relapse activity over 5 years (absolute difference of 1
451 relapse per 50 patient-years). In none of the comparisons did the superior effect of AHSC
452 translate into reducing the risk of disability worsening. On the other hand, AHSC was

453 associated with partial recovery from the previously accumulated neurological disability when
454 compared with fingolimod and natalizumab. Interestingly, we did not find evidence of
455 difference between the effects of AHSCT and ocrelizumab on relapses, studied over a
456 shorter, 3-year follow-up. The observation that AHSCT showed superiority in clinical
457 outcomes over fingolimod and, to a lesser extent, natalizumab, but not ocrelizumab, is
458 intriguing. While this may be attributed to the shorter on-treatment follow-up available in the
459 ocrelizumab cohort, another explanation may relate to the differences in the mechanisms of
460 action among the therapies. Fingolimod and natalizumab are antitrafficking agents,
461 sequestering lymphocytes outside of the CNS, whereas ocrelizumab acts through depletion
462 of CD20-positive cells – a mechanism that is more similar to the immunosuppressive effect of
463 AHSCT.³⁴

464 The safety profile of AHSCT is consistent with the previous cohort experience. A
465 considerable number of patients experienced febrile neutropenia during mobilisation with
466 cyclophosphamide and 9% required ICU admission. Doses lower than 2g/m² are associated
467 with a lower risk of this complication. Whether the lymphodepleting effect of
468 cyclophosphamide is dose-dependent and whether the mononuclear content of the graft
469 impacts on the outcome is unknown. Almost one third of patients developed infectious
470 complications at later stages, following recovery from the transplant procedures. Only one
471 treatment-related death (0.6%) was reported.

472 The main limitation of this study is its lack of true randomisation. However, randomisation to
473 AHSCT or DMT with appropriate blinding is extremely problematic, given the considerably
474 different intensities of treatment protocols, persistence and safety profiles.³⁵ It has therefore
475 been argued that observational data analysed with appropriate statistical methodology
476 represent an optimal solution to establishing evidence for comparative effectiveness of
477 AHSCT.³⁶ We have utilised well-established methods to emulate clinical trials using a large
478 composite database of patients treated with AHSCT or DMTs, and this provides this study
479 with larger power and generalisability than the previous randomised trials.¹⁷ We have applied
480 matching, pairwise censoring and model adjustment to mitigate the potential biases, an

481 approach whose validity was demonstrated in our previous studies.^{12,37} As the result of strict
482 inclusion and matching criteria, we achieved a close alignment of the compared treatment
483 groups on their demographic and clinical characteristics. While the study did not allow direct
484 comparison of the safety for AHSCT and the DMTs, the systematic acquisition of safety
485 information in the AHSCT cohort enabled us to report short- and long-term safety outcomes
486 of AHSCT. Because MRI information was unavailable in more than half of the AHSCT cohort,
487 this study did not include MRI in matching or as one of its outcomes. However, the MRI
488 characteristics at baseline were similar between the matched groups where the information
489 was available. Our previous studies did not show any effect of inclusion of MRI in matching
490 on their results.^{11,12} To account for geographic differences in cohorts and outcomes,³⁸ we
491 have matched patients on their geographic location. Some of the patients in the AHSCT
492 group would be followed as part of open-label clinical trials. To mitigate this potential source
493 of ascertainment bias, we have accounted for differences in follow-up, we have adjusted
494 models for the frequency of visits with EDSS scores. To explore the specific effectiveness of
495 conditioning regimens on the effectiveness of AHSCT, a dedicated study with specific design
496 will be required.

497 We show that over 5 years, the effect of AHSCT on suppressing relapses and facilitating
498 recovery from disability in highly active relapsing-remitting MS is superior to fingolimod and
499 natalizumab. Over the limited follow-up 3 years, we did not find its clinical effect superior to
500 that of ocrelizumab. Even though AHSCT requires a complex treatment procedure, its one-
501 off nature may offer practical advantages over the continuously administered therapies.⁸
502 AHSCT is associated with considerable risks, but the risk of treatment-associated mortality is
503 low.

504

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520

521 **Authors' contributions**

522 Tomas Kalincik conceptualised and designed the study, recruited patients, contributed data,
523 carried out statistical analysis, interpreted the results, have drafted and edited the
524 manuscript. Mark S. Freedman, Harold Atkins, Joachim Burman, Jennifer Massey, Ian
525 Sutton, Barbara Withers, Richard Macdonell, Andrew Grigg, Oivind Torkildsen, Lars Bo,
526 Anne Kristin Lehmann, Basil Sharrack, John Snowden conceptualised the study, recruited
527 patients, contributed data, interpreted the results and have edited the manuscript. Sifat
528 Sharmin, Izanne Roos interpreted the results and have edited the manuscript. Eva Kubala
529 Havrdova, Eva Krasulova, Marek Trnny, Tomas Kozak, Anneke van der Walt, Helmut
530 Butzkueven, Pamela McCombe, Olga Skibina, Jeannette Lechner-Scott, Barbara Willekens,
531 Elisabetta Cartechini, Serkan Ozakbas, Raed Alroughani, Jens Kuhle, Francesco Patti,
532 Pierre Duquette, Alessandra Lugaresi, Samia J. Khoury, Mark Slee, Recai Turkoglu,
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534 Oliver Gerlach, Guy Laureys, Liesbeth Van Hijfte, Rana Karabudak, Daniele Spitaleri, Tunde
535 Csepany, Riadh Gouider, Saloua Mrabet, Tamara Castillo Triviño, Justin Garber, Jose Luis
536 Sanchez-Menoyo, Eduardo Aguera-Morales, Yolanda Blanco, Abdullah Al-Asmi, Bianca
537 Weinstock-Guttman, Bruce Taylor, Yara Fragoso, Koen de Gans, Allan Kermode recruited
538 patients, contributed data, interpreted the results and have edited the manuscript.

539

540 **DATA SHARING STATEMENT**

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

548

549 **DECLARATION OF INTERESTS**

550 Tomas Kalincik served on scientific advisory boards for BMS, Roche, Janssen, Sanofi
551 Genzyme, Novartis, Merck and Biogen, steering committee for Brain Atrophy Initiative by
552 Sanofi Genzyme, received conference travel support and/or speaker honoraria from WebMD
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560 Mark Freedman received research/educational grants from Sanofi-Genzyme Canada,
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563 Novartis, Sanofi-Genzyme, Teva Canada Innovation. He served as a member of company
564 advisory boards or boards of directors for Alexion, Atara Biotherapeutics, Bayer Healthcare,
565 Beigene, BMS (Celgene), Celestra Health, Hoffman La-Roche, Janssen (J&J), McKesson,
566 Merck Serono, Novartis, Sanofi-Genzyme and participated in company sponsored speaker's
567 bureau for Sanofi-Genzyme and EMD Serono.
568 Harold Atkins has nothing to disclose.
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570 Ian Sutton received compensation for an educational activity from Biogen.
571 Barbara Withers has nothing to disclose.
572 Jennifer Massey served on scientific advisory board for Roche, received conference travel
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577 Oivind Torkildsen received speaker honoraria from and served on scientific advisory boards
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- 808

809

810 **FIGURE LEGENDS**

811

812 **Figure 1**

813 Consort diagram of patient disposition

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

816

817 **Figure 2**

818 Comparative effectiveness of AHSCT and fingolimod

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

821

822 **Figure 3**

823 Comparative effectiveness of AHSCT and natalizumab

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

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828 **Figure 4**

829 Comparative effectiveness of AHSCT and ocrelizumab

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

832

833 **Table 1**834 **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

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839 The patient characteristics are presented for each pair of matched treatment groups separately.

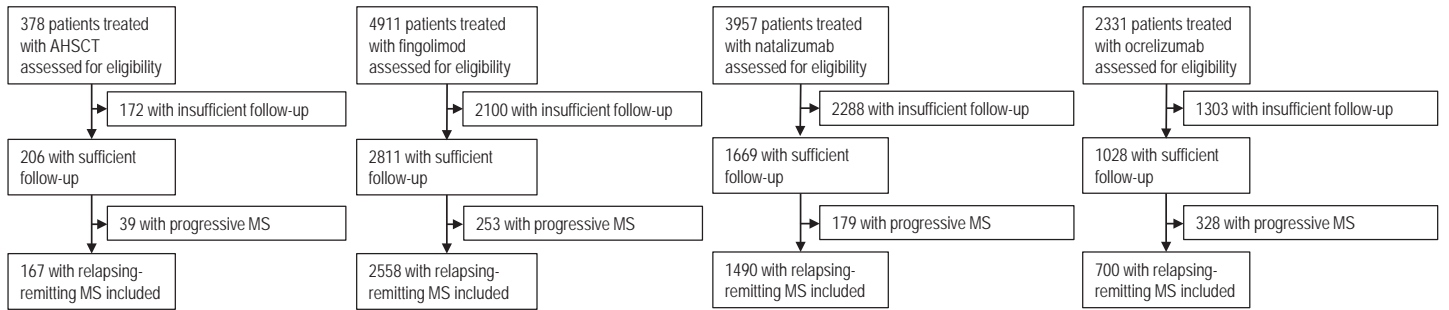
840 d, standardised difference (Cohen's d); SD, standard deviation; EDSS, Expanded Disability Status Scale; IQR, interquartile range

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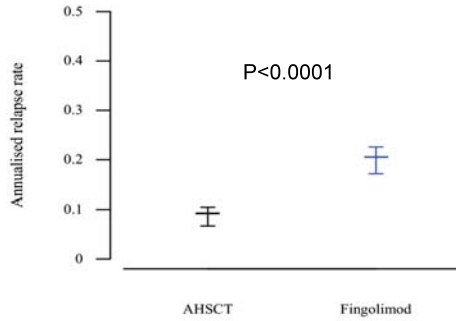
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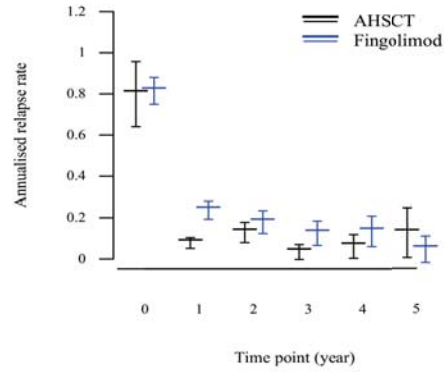
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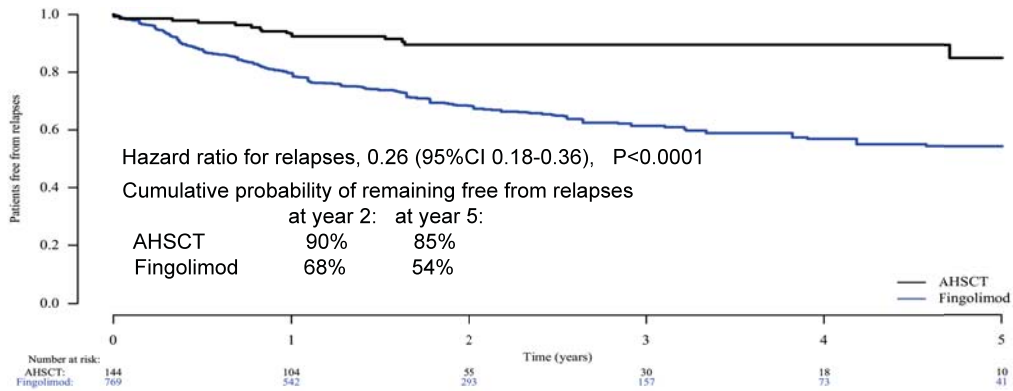
A Overall annualised relapse rate



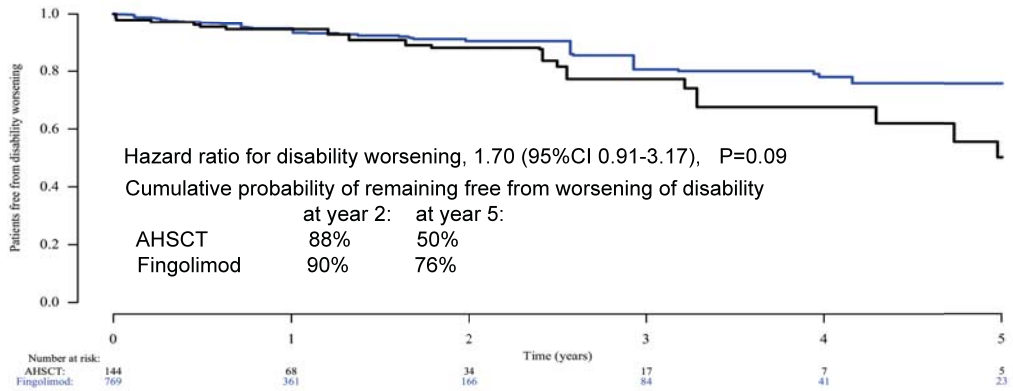
B Annual relapse rate by year



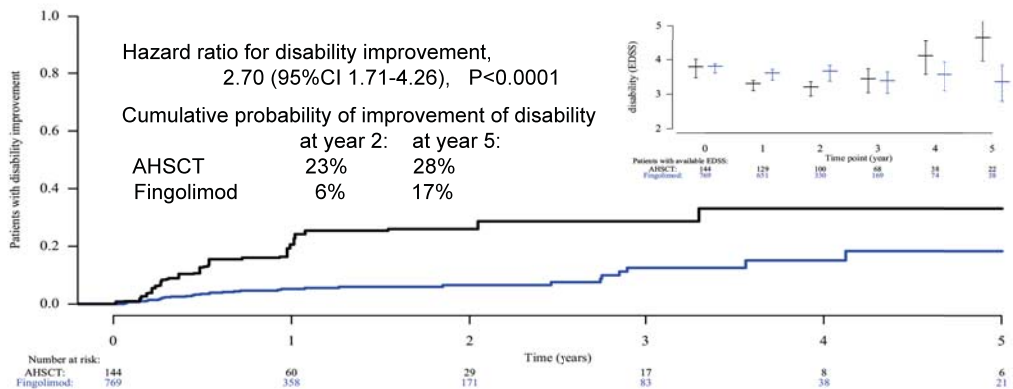
C Freedom from relapses



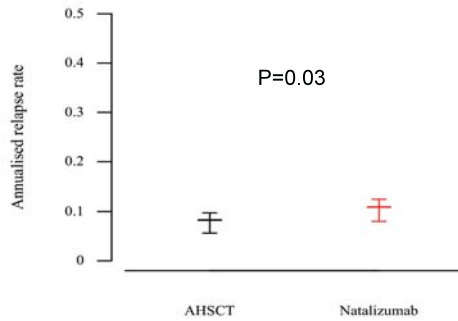
D Confirmed disability worsening



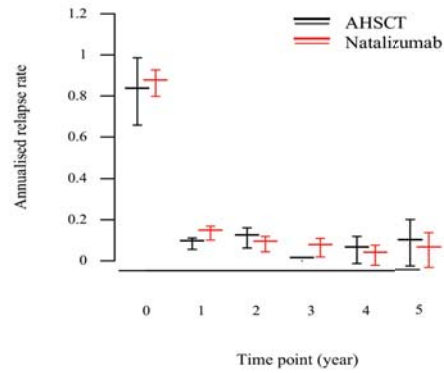
E Confirmed disability improvement



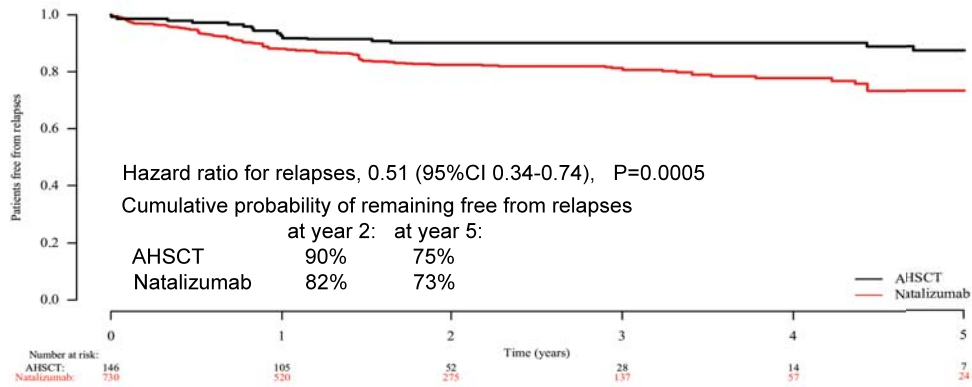
A Overall annualised relapse rate



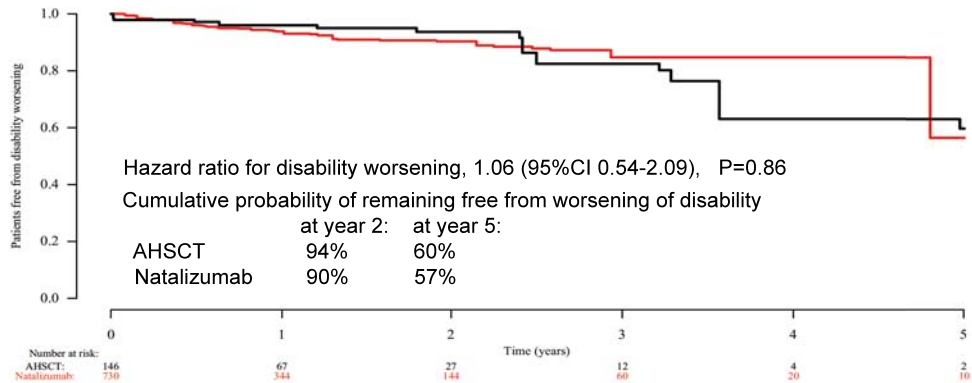
B Annual relapse rate by year



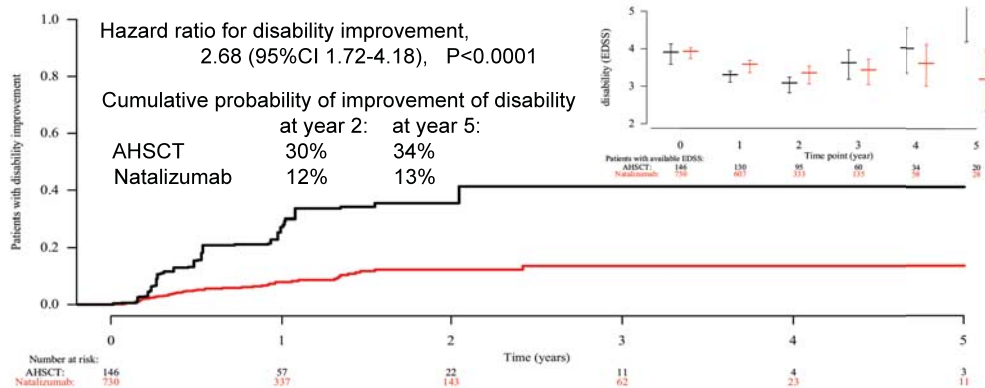
C Freedom from relapses



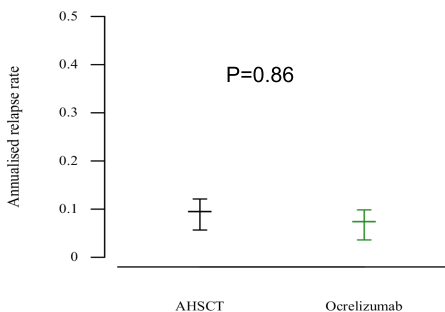
D Confirmed disability worsening



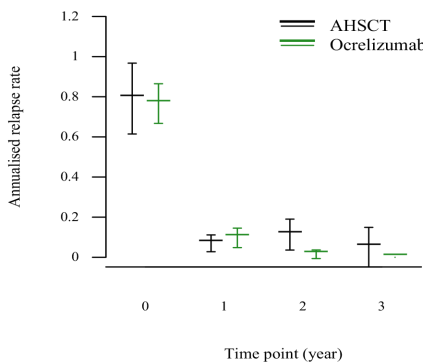
E Confirmed disability improvement



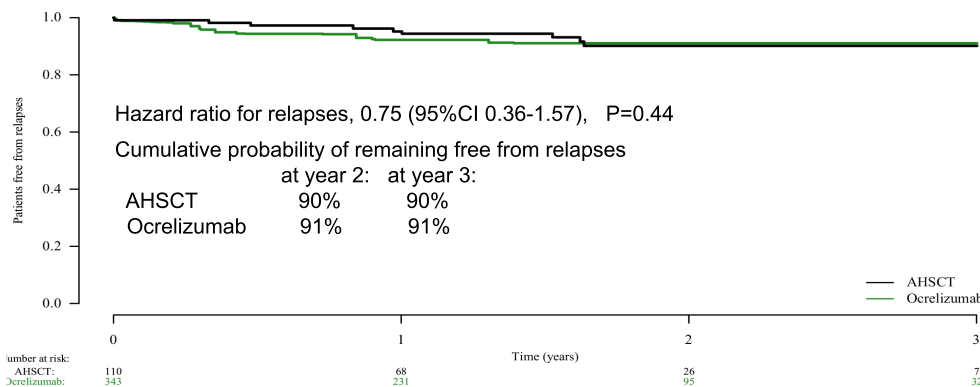
A Overall annualised relapse rate



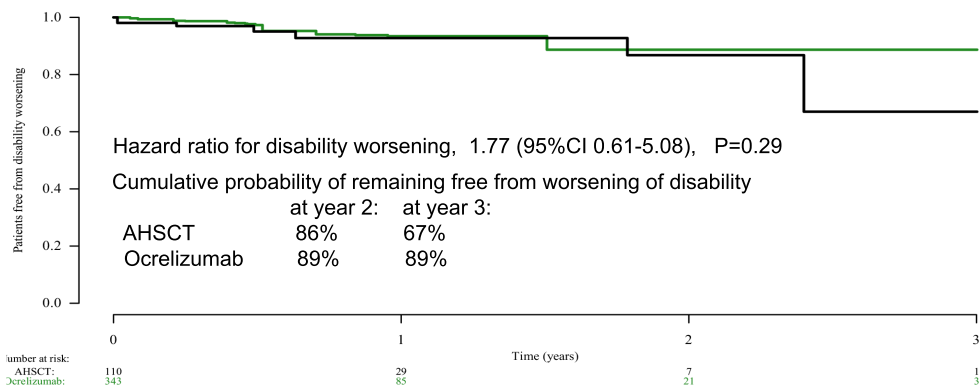
B Annual relapse rate by year



C Freedom from relapses



D Confirmed disability worsening



E Confirmed disability improvement

