1 **Title :**
2 **Effectiveness of autologous haematopoietic stem cell transplantation versus**
3 **fingolimod, natalizumab and ocrelizumab in highly active relapsing-remitting multiple**
4 **sclerosis**
5
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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±SD 0.09±0.30 vs. 0.20±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±0.31 vs. 0.10±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 AHSCT 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 AHSCT were included.

276

277 **Procedures**

278 Patients received AHSCT following protocols specific to the treating centres.[2,3,5,23]

279 Autologous haematopoietic stem cells were mobilised using cyclophosphamide 2-4.5 g/m^2 IV

280 with granulocyte colony stimulating factor 5-10μg/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/m^2, etoposide 200-

286 800mg/m^2, cytarabine 200mg/m^2 and melphalan 140mg/m^2), 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   ARRs 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 Γ.[31] Where no evidence of difference between the

344 compared groups was found, the minimum detectable effect at α=0.05 and 1-β=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 ≤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±standard deviation [SD] 0.09±0.30 vs. 0.20±0.44, respectively,

370   p<0.0001). This observation was robust to unmeasured confounding (Γ>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 (Γ=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 (Γ=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 AHSCT with the same number randomised to

426   escalation of DMT.[7] The trial reported superiority of AHSCT 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 AHSCT head-to-head with the most

431   potent available DMTs.

432   Presently, three randomised clinical trials comparing AHSCT (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 AHSCT 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 AHSCT versus

438   a composite comparator of ocrelizumab or alemtuzumab. In addition, two randomised trials

439   are comparing AHSCT 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 AHSCT 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   AHSCT 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   AHSCT is presently considered – highly inflammatory disease in young patients with prior

447   failures of potent DMTs and mild-moderate disability. With the comparison of AHSCT against

448   fingolimod we have established discriminative ability of the matched analysis, clearly

449   demonstrating the expected superiority of AHSCT. In comparison to natalizumab, AHSCT

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 AHSCT

452   translate into reducing the risk of disability worsening. On the other hand, AHSCT 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   sequestrating 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/m^2 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

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.

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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
826
827
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

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		4911 patients treated with fingolimod assessed for eligibility		3957 patients treated with natalizumab assessed for eligibility		2331 patients treated with ocrelizumab assessed for eligibility

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

P<0.0001

B Annual relapse rate by year

C Freedom from relapses

Hazard ratio for relapses, 0.26 (95%CI 0.18-0.36), P<0.0001
Cumulative probability of remaining free from relapses

	at year 2:	at year 5:
AHSCT	90%	85%
Fingolimod	68%	54%

Number at risk:

	0	1	2	3	4	5
AHSCT:	144	104	55	30	18	10
Fingolimod:	769	542	293	157	73	41

D Confirmed disability worsening

Hazard ratio for disability worsening, 1.70 (95%CI 0.91-3.17), P=0.09
Cumulative probability of remaining free from worsening of disability

	at year 2:	at year 5:
AHSCT	88%	50%
Fingolimod	90%	76%

Number at risk:

	0	1	2	3	4	5
AHSCT:	144	68	34	17	7	5
Fingolimod:	769	361	166	84	41	23

E Confirmed disability improvement

Hazard ratio for disability improvement,
   2.70 (95%CI 1.71-4.26), P<0.0001
Cumulative probability of improvement of disability

	at year 2:	at year 5:
AHSCT	23%	28%
Fingolimod	6%	17%

Patients with available EDSS

	0	1	2	3	4	5
AHSCT:	144	129	100	68	38	22
Fingolimod:	769	651	330	169	74	38

Number at risk:

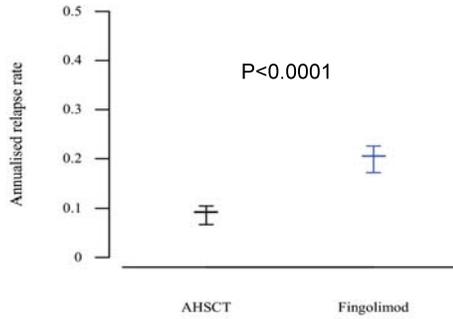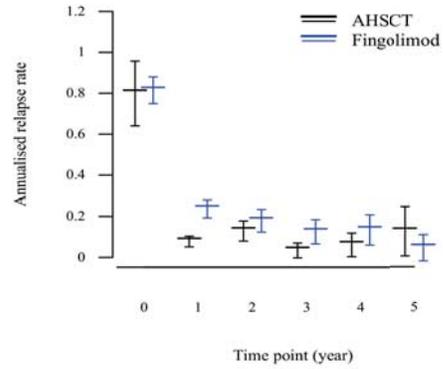|	0	1	2	3	4	5
AHSCT:	144	60	29	17	8	6
Fingolimod:	769	358	171	83	38	21

A Overall annualised relapse rate

P=0.03

Annualised relapse rate

AHSCT   Natalizumab

B Annual relapse rate by year

AHSCT
Natalizumab

Annualised relapse rate

Time point (year)

C Freedom from relapses

Patients free from relapses

Hazard ratio for relapses, 0.51 (95%CI 0.34-0.74),   P=0.0005
Cumulative probability of remaining free from relapses
                        at year 2:   at year 5:
        AHSCT   90%   75%
        Natalizumab   82%   73%

AHSCT
Natalizumab

Time (years)

Number at risk:
AHSCT: 146   105   52   28   14   7
Natalizumab: 730   520   275   137   57   24

D Confirmed disability worsening

Patients free from disability worsening

Hazard ratio for disability worsening, 1.06 (95%CI 0.54-2.09),   P=0.86
Cumulative probability of remaining free from worsening of disability
                        at year 2:   at year 5:
        AHSCT   94%   60%
        Natalizumab   90%   57%

Time (years)

Number at risk:
AHSCT: 146   67   27   12   4   2
Natalizumab: 730   344   144   60   20   10

E Confirmed disability improvement

Patients with disability improvement

Hazard ratio for disability improvement,
        2.68 (95%CI 1.72-4.18),   P<0.0001

Cumulative probability of improvement of disability
                        at year 2:   at year 5:
        AHSCT   30%   34%
        Natalizumab   12%   13%

disability (EDSS)

Time point (year)

Patients with available EDSS:
AHSCT: 146   130   95   60   34   20
Natalizumab: 730   607   353   155   54   24

Time (years)

Number at risk:
AHSCT: 146   57   22   11   4   3
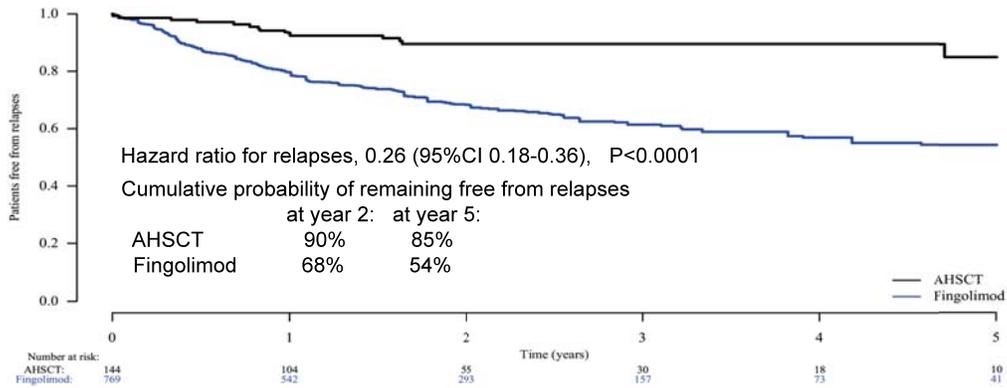Natalizumab: 730   337   143   62   23   11

A Overall annualised relapse rate

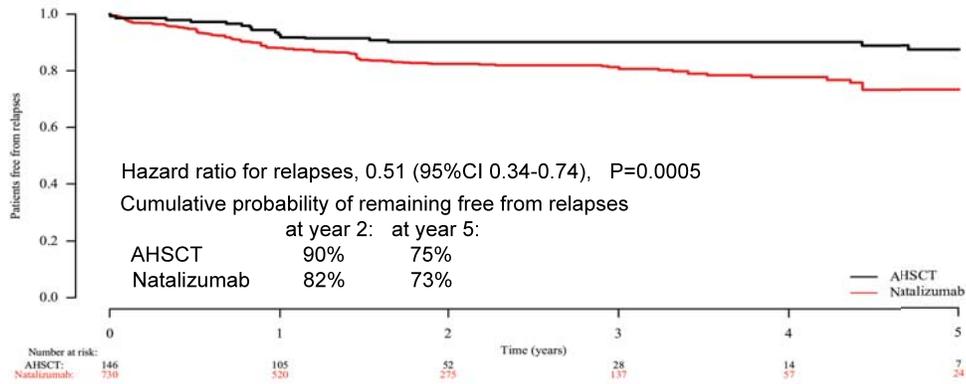**B** Annual relapse rate by year

C Freedom from relapses

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%

Number at risk:
AHSCT: 110 68 26 7
Ocrelizumab: 343 231 95 32

D Confirmed disability worsening

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%

Number at risk:
AHSCT: 110 29 7 1
Ocrelizumab: 343 85 21 3

E Confirmed disability improvement

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%

Patients with available EDSS:
AHSCT: 110 93 51 27
Ocrelizumab: 343 289 101 43

Number at risk:
AHSCT: 110 26 6 1
Ocrelizumab: 343 86 21 3