Autologous hematopoietic stem cell transplantation in multiple sclerosis

A meta-analysis

Maria Pia Sormani, PhD
Paolo A. Muraro, MD
Irene Schiavetti, PhD
Alessio Signori, PhD
Alice Laroni, MD
Riccardo Saccardi, MD
Gian Luigi Mancardi, MD

Correspondence to Dr. Sormani: mariapia.sormani@unige.it

ABSTRACT

Objective: To summarize the evidence on immunoablative therapy followed by autologous hematopoietic stem cell transplantation (aHSCT) to manage severe and treatment-refractory multiple sclerosis (MS).

Methods: We collected all the published studies of aHSCT in any form of MS from 1995 to 2016, carefully excluding reports that were updated in subsequent studies. Endpoints were transplant-related mortality (TRM), rate of disease progression, and no evidence of disease activity (NEDA) status. A weighted metaregression based on a Poisson model was run, assessing whether there were study-specific characteristics with an effect on TRM and progression.

Results: Fifteen studies including 764 transplanted patients were pooled in the meta-analysis. The pooled estimate of TRM was 2.1% (95% confidence interval [CI] 1.3%–3.4%). TRM was higher in older studies ($p = 0.014$) and in studies with a lower proportion of patients with relapsing-remitting MS (RRMS) ($p = 0.028$). A higher baseline Expanded Disability Status Scale ($p = 0.013$) was also significantly associated with a higher TRM. Pooled rate of progression was 17.1% at 2 years (95% CI 9.7%–24.5%) and 23.3% (95% CI 16.3%–31.8%) at 5 years. Lower 2-year progression rate was significantly associated with higher proportions of patients with RRMS ($p = 0.004$). The pooled proportion of NEDA patients at 2 years was 83% (range 70%–92%) and at 5 years was 67% (range 59%–70%).

Conclusions: The emerging evidence on this therapeutic approach in MS indicates that the largest benefit/risk profile form this therapeutic approach can be obtained in patients with aggressive MS with a relapsing-remitting course and who have not yet accumulated a high level of disability.

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GLOSSARY

aHSCT = autologous hematopoietic stem cell transplantation; **ARR** = annualized relapse rate; **ASTIMS** = Autologous Hematopoietic Stem Cell Transplantation Trial in MS; **CI** = confidence interval; **DMT** = disease-modifying therapy; **EBMT** = European Society for Blood and Marrow Transplantation; **EDSS** = Expanded Disability Status Scale; **IFN** = interferon; **MS** = multiple sclerosis; **NEDA** = no evidence of disease activity; **RRMS** = relapsing-remitting multiple sclerosis; **SPMS** = secondary progressive multiple sclerosis; **TRM** = transplant-related mortality.

Multiple sclerosis (MS) is an inflammatory, putatively autoimmune disease and is the most common demyelinating disease in countries of European ancestry. Disease-modifying therapies (DMT) targeting inflammation have been shown to reduce the disease activity in patients with relapsing-remitting MS (RRMS). However, there are currently no approved medications that can effectively prevent, reverse, or stabilize the progressive phase that often follows RRMS, i.e., secondary progressive MS (SPMS), or that occurs from onset in patients with primary progressive MS. Furthermore, some patients with RRMS have an aggressive course and do not respond to conventional DMT.

Against this scenario, immunoablative therapy followed by autologous hematopoietic stem cell transplantation (aHSCT) has been investigated for the last 2 decades to manage severe and treatment-refractory MS.[1,2] The hypothesis on which aHSCT is based is that the intense

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From the Departments of Health Sciences (M.P.S., I.S., A.S.) and Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Maternal and Child Health (A.L., G.L.M.), University of Genoa, Italy; Division of Brain Sciences (P.A.M.), Imperial College, London, UK; IRCCS Azienda Ospedaliera Universitaria San Martino-IST (A.L., G.L.M.), Genoa; and Cell Therapy and Transfusion Medicine Unit (R.S.), Careggi University Hospital, Firenze, Italy.

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immunosuppression eliminates the hyperactive immune system, causing an immune reset: a new autotolerant immunity should arise after aHSCT, with a better control of any disease-related cells.[3] Almost all the studies evaluating aHSCT in MS were open-label, single-arm, observational cohort studies; only one comparative phase II randomized clinical trial assessing the effect of aHSCT vs mitoxantrone in aggressive RRMS or SPMS has been published (Autologous Hematopoietic Stem Cell Transplantation Trial in MS [ASTIMS] trial).[4]

The aims of this analysis were to quantitatively collect and summarize all the evidence published about the outcomes after aHSCT for treatment of MS and to evaluate the effect of patient-related and procedure-related variables on these outcomes.

METHODS

Search strategy and selection criteria. We collected all the published studies reporting aHSCT for MS from January 1995 to July 2016 by searching PubMed. We used search terms for the disease name (multiple sclerosis, demyelinating disease), treatment (transplant, autologous hematopoietic stem cell transplantation), and MeSH terms used for indexing articles for MEDLINE/PubMed (multiple sclerosis [MeSH] and transplantation [MeSH] and humans [MeSH]). Trials fulfilling the following inclusion criteria were included: any study in MS, assessing the efficacy of aHSCT, including more than 5 patients, reporting data on mortality and on the clinical follow-up, in English language. The abstracts were independently screened by 3 authors (I.S., A.S., M.P.S.) and full articles were examined if relevant information could not be ascertained from the abstracts. We excluded studies that were updated in subsequent reports if it was explicitly stated, or after contacting the investigators when it was not clearly specified in the Methods. The criterion for selecting a study with overlapping patients was to choose the larger one.

Data extraction. Data extraction was done independently by 3 authors (I.S., A.S., M.P.S.) and the accuracy of extraction was validated by consensus. For each trial, data on year of publication, number of enrolled patients, baseline characteristics (age, Expanded Disability Status Scale [EDSS], proportion of patients with RRMS, relapses in the previous year, number of previous drugs), and follow-up information (mortality, disease activity, EDSS) were collected.

Endpoints. The following mortality outcomes were collected: transplant-related mortality (TRM) defined as death within 100 days of aHSCT, first year mortality rate, second year mortality rate, and overall study-specific mortality rate.

Progression events were defined according to an increase of EDSS score (1 point for baseline EDSS $\leq$5.5, 0.5 points for baseline EDSS $>$5.5, confirmed at 6 or 12 months). Patients were defined as presenting no evidence of disease activity (NEDA) over a given period of time if they did not experience any clinical relapse, disability progression, or any new MRI lesion (T2 or gadolinium-enhancing) over that period.

Studies' characteristics classification. Studies were grouped according to baseline demographics and clinical characteristics (above and below the weighted mean values of the entire cohort, table 1 and table e-1 at Neurology.org) and according to aHSCT

Table 1 Baseline demographics and clinical characteristics of each included study

Authors	Sample size, n	Follow-up, mo, median (range)	Age, y, median (range)	EDSS, median (range)	RRMS, %	MS duration, y, median (range)	Regimen intensity[a]
Burt et al.[7]	21	25 (6-60)	39 (21-52)	7.0 (3.0-8.5)	33	7 (0.8-15)	High
Samijn et al.[8]	14	36 (7-36)	35 (23-59)	6.0 (5.0-6.5)	0	5 (2-12)	High
Saccardi et al.[9]	178	41.7 (6-118)	34 (18-58)	6.5 (4-9)	22	6.7 (0.2-27)	Mixed
Hamerschlak et al.[10]	41	36 (NA)	42 (27-53)	6.5 (4.0-7.0)	10	NA (2-22)	Mixed
Xu et al.[11]	36	48.9 (10-91)	35 (20-51)	6.5 (4.5-9.0)	0	6 (0.6-28)	Intermediate
Bowen et al.[12]	26	48 (3-72)	41 (27-60)	7.0 (5.0-8.0)	4	7 (0.8-23)	High
Chen et al.[13]	25	59.6 (4.5-111)	37.3 (15-64)	8.0 (3.0-9.5)	20	4 (0.6-12.3)	Intermediate
Mancardi et al.[14]	74	48.3 (0.8-126)	35.7 (16-53)	6.5 (4.0-9.0)	45	11.2 (1-28)	Intermediate
Burman et al.[15]	41	47.4 (12-108)	31 (9-52)	6.0 (1.0-8.5)	85	6.3 (0.3-25)	Intermediate
Burt et al.[16]	145	24 (0.5-60)	37 (18-60)	4.0 (3.0-5.5)	81	5.1 (0.8-22)	Low
Currò et al.[17]	7	60 (60-60)	28 (23-38)	6.0 (5.0-7.0)	100	6.5 (4-12)	Low
Mancardi et al.[4,b]	9	48.3 (0.8-126)	36 (22-46)	6.5 (5.5-6.5)	22	10.5 (2-23)	Intermediate
Nash et al.[18]	24	46.5 (44-62.5)	38 (27-53)	4.5 (3.0-5.5)	100	4.9 (0.6-12)	Intermediate
Shevchenko et al.[19]	99	48.9 (0.2-98)	34.6 (18-54)	3.5 (1.5-8.5)	46	5 (0.5-24)	Intermediate
Atkins et al.[20]	24	80.4 (24-156)	34 (24-45)	5 (3-6)	50	7.5 (1.7-21.2)	High
Overall[c]	764	42.1 (41.2-43.0)	35.7 (35.5-35.9)	5.6 (5.5-5.7)	44 (40-48)	6.5 (6.3-6.8)	

Abbreviations: EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; NA = not available; RRMS = relapsing-remitting multiple sclerosis.
[a] For the regimen intensity classification, see text.
[b] Subset of patients treated with autologous hematopoietic stem cell transplantation (ref).
[c] Pooled mean of the reported summary measures weighted by study size.

methodology used. Characteristics considered were age at transplant (above and below 36 years), baseline EDSS (above and below 5.5), and proportion of patients with RRMS (above and below 44%). Studies were also grouped according to the year of transplant (before and during/after 2005). This cutoff value was chosen as the one better discriminating studies: in 7 out of 15 studies, all the patients were transplanted before 2005, and in 3 studies, all the patients were transplanted after 2005. The 5 studies with years of transplant crossing 2005 were classified according the median value of the interval of time in which transplant was performed (e.g., if patients were transplanted between 2003 and 2014, the study was classified as post-2005). The conditioning regimen intensity was classified as low, intermediate, or high intensity according to the guidelines of the European Society for Blood and Marrow Transplantation (EBMT).[5] In principle, regimens including either high-dose busulfan or total body irradiation were classified as high-intensity. Regimens based on cyclophosphamide only were classified as low-intensity; all the others were considered as intermediate intensity (table e-2).

Statistical methods. The number of deaths was extracted from each study along with the time of death relative to transplant date. A pooled estimate of TRM was obtained by dividing the number of TRM deaths for the number of transplanted patients. Pooled year 1 and year 2 overall mortality rates were estimated by dividing the number of year 1 and year 2 deaths by the number of patients at risk at year 1 and year 2, respectively. Overall mortality was estimated by dividing the total number of deaths observed over the whole follow-up for the total number of patient-years. Heterogeneity among studies was evaluated by the Q χ^2 and I^2 statistics. A Poisson regression model was used to run a meta-regression assessing whether there were study-specific characteristics with a relevant effect on TRM. The factors examined were year of transplant, baseline EDSS, age, proportion of patients with RRMS included in the study, and conditioning regimen intensity class. Summary estimates of progression rate at year 2 and 5 were extracted when reported or estimated from the available data and figures (Kaplan-Meier survival curves) and summarized as actuarial proportions. The standard error of the estimate was derived from the asymptotic variance of log–log transformation of progression.[6] A pooled estimate of progression rate was obtained by a random-effects meta-regression model. The same model was used to assess whether there were study-specific characteristics with a relevant effect on the rate of progression at year 2 and at year 5.

The cumulative proportion of NEDA patients over time was extracted when available along with the number of patients at risk at each time point. A pooled estimate of the proportion of NEDA patients over time was calculated by weighting for the number of patients at risk in each study.

Standard protocol approvals, registrations, and patient consents. All the articles stated that the original raw data collections were approved by the local ethics committees at all centers and written informed consent was obtained from all study patients. No personally identifiable patient data were accessed in our meta-analysis study.

RESULTS

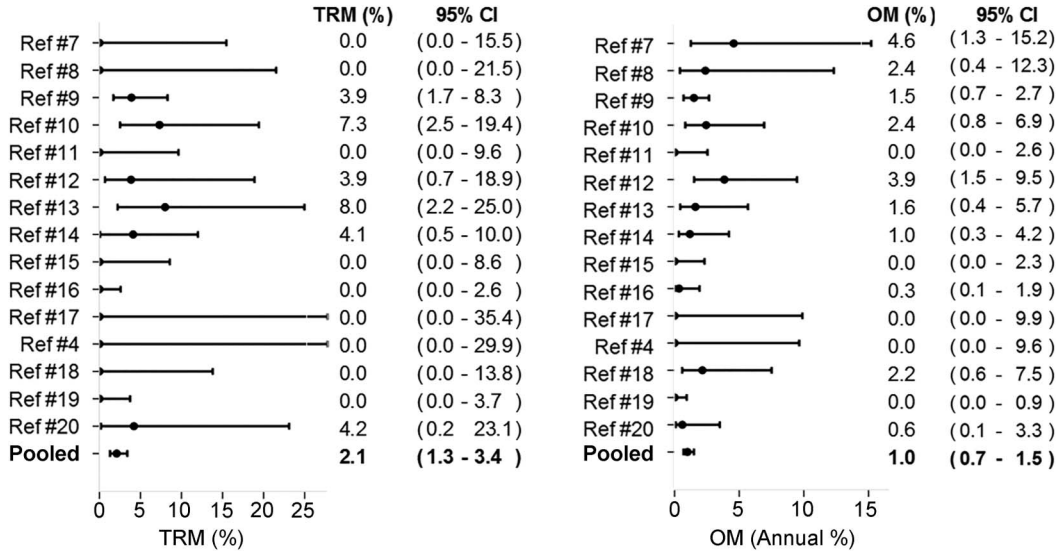
Trials included in the analysis. The PubMed search retrieved 140 articles published between January 1995 and April 2016. A total of 122 articles were excluded and reasons for exclusion were as follows: studies including less than 5 cases (6 articles), lack of clinical data (71 articles), or studies reporting cases included in other (larger or more recent) studies (46 articles). Eighteen studies were identified [4,7–23] (figure e-1). We excluded 3 further studies[21–23] since they contained data on patients reported in a more recent report.[8] We re-analyzed the individual patient data of a randomized trial (ASTIMS[4]) evaluating aHSCT vs mitoxantrone; the aHSCT arm included 9 patients, while the mitoxantrone arm (including 11 patients) was excluded. A final set of 15 studies of aHSCT for the treatment of MS was analyzed, including a total of 764 transplanted patients, contributing information on 2,680 patient-years.

Patient population. The selected studies, along with the baseline characteristics and the number of patients included, are reported in table 1. The median follow-up time was 41.7 months (range 24–80.4 months). Baseline EDSS ($p < 0.001$), disease duration ($p = 0.08$), and the proportion of patients with progressive MS ($p < 0.001$) were lower in more recent reports (classified as post-2005 studies; supplementary appendix). Fourteen out of 15 studies were open-label uncontrolled studies, 1 was the experimental arm of a randomized study (ASTIMS[4]); 5 studies were retrospective, whereas 10 were assessed prospectively.

Transplant characteristics. Of the 15 studies in this analysis, 4 used a high-intensity regimen,[7,8,12,20] including either total body irradiation or busulfan, while in 2 a low-intensity regimen was employed.[16,17] One study used a low-intensity regimen for half of the patients and an intermediate regimen for the other half.[10] All other studies used an intermediate-intensity regimen, mostly represented by the association of BCNU, etoposide, Ara-C, and melphalan (BEAM regimen). In most of the reported cases a serotherapy, such as anti–T-lymphocyte polyclonal serum, was added to the conditioning regimen to potentiate the immunosuppression. In all studies except one, mobilized peripheral blood-derived stem cells were used.

Transplant-related mortality and overall mortality. In the pooled cohort of 764 transplanted patients, there were 16 transplant-related deaths. The pooled estimate of TRM was 2.1% (95% confidence interval [CI] 1.3%–3.4%), with some degree of heterogeneity among studies ($I^2 = 37\%$, $p = 0.07$) (figure 1). No other deaths occurred during the first year after transplant. The mortality during the second year after transplant was 0.9% (95% CI 0.4%–2.1%, heterogeneity $I^2 = 0\%$, $p = 0.45$). In the pooled cohort, 28 deaths were observed over 2,680 patient-years, for an average annualized mortality rate of 1.0% (95% CI 0.7%–1.5%, heterogeneity $I^2 = 53.5\%$, $p = 0.007$) (figure 1).

Figure 1 Forest plot for transplant-related mortality (TRM, defined as the number of deaths occurring within 100 days from transplant divided by the number of transplanted patients) and annualized overall mortality (OM, defined as the total number of deaths reported divided by the number of patient-years) in each study and pooled estimates

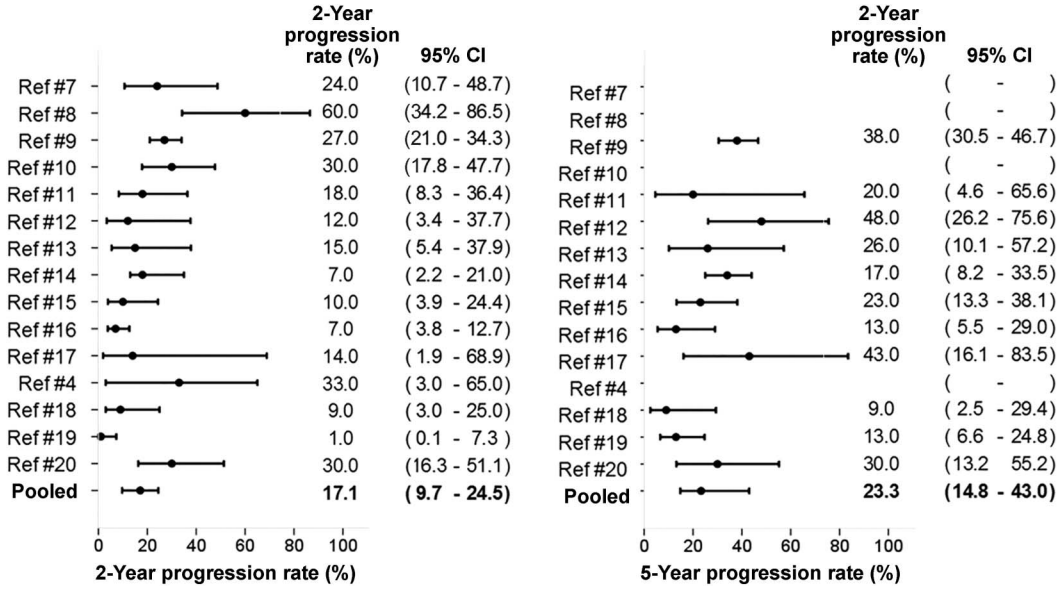


CI = confidence interval.

The probability of TRM was associated with the year of transplant: only 1 death (TRM 0.3%, 95% CI 0%–2.0%) was reported among the 349 patients transplanted post-2005 (7 studies), as compared to a TRM of 3.6% (95% CI 2.2%–6.0%, p for interaction = 0.014) observed among the 415 patients transplanted in the 8 older studies (figure 1). TRM probability was also significantly associated with the disease type at the time of transplant: studies including a larger proportion of patients with RRMS had a TRM = 1.0% (95% CI 0.4%–2.6%), while those with a lower proportion of RRMS had a TRM = 3.4% (95% CI 1.9%–6.0%, p for interaction = 0.028). A higher baseline EDSS ($p = 0.001$) was also significantly associated with a higher TRM (figure 2). There was no significant association of TRM with age and regimen intensity (no TRM was observed among the 119 patients treated with low-intensity regimens).

All deaths and causes of mortality are reported in table e-3.

Figure 2 Forest plot for 2 years and 5 years progression rate in each study and pooled estimates



CI = confidence interval.

Rate of disability progression. Pooled rates of disability progression were 17.1% at 2 years (95% CI 9.7%–24.5%, $I^2 = 83.3\%$, $p < 0.001$) and 23.3% (95% CI 16.3%–31.8%, heterogeneity $I^2 = 69\%$, $p < 0.001$) at 5 years (figure 2). The heterogeneity among studies was high. The only factor significantly associated with a lower probability of disability progression after 2 years was RRMS disease course (figure 3): the pooled rate of 2-year progression in studies including less than 44% patients with RRMS was 24.8% (95% CI 16.7%–32.9%) vs 7.8% (95% CI 1.3%–14.2%, p for interaction = 0.004) in studies including more than 44% of RRMS patients. This analysis was not able to demonstrate an effect of regimen intensity on the risk of progression (figure 3).

Annualized relapse rate (ARR). The number of relapses after aHSCT was reported in 11 out of the 15 included studies. The pooled ARR post-aHSCT was 0.037 (95% CI 0.028–0.047, range 0–0.19), but there was high heterogeneity across studies ($I^2 = 76\%$, $p < 0.001$, figure e-2).

Proportion of NEDA. An analysis of the proportion of patients who were NEDA during the follow-up was reported in 5 studies[9,14,15,17,19] (274 patients). The proportion of NEDA patients 2 years after transplant was 83.4% (range 70%–92%). After 5 years from transplant, data were available in 4 studies (n = 233 patients): the proportion of 5-year NEDA patients was 67% (range 59%–70%) (figure 4).

DISCUSSION A recent surge of original reports of outcomes in patients with MS treated with aHSCT[16–20] has energized the debate about this therapeutic approach for aggressive forms of MS. With this meta-analysis, we aim to provide useful information on the published evidence. All but one[4] of the studies included in this meta-analysis are single-arm studies assessing the medium to long-term effect of aHSCT in differently selected and treated groups of patients with MS. Extracting definitive information about the efficacy of aHSCT, and in particular, understanding its relative efficacy as compared to the other approved therapies in MS, is difficult for a number of reasons.

First, the aHSCT procedure is not uniform across studies, but as discussed, there are important differences in the transplant technology, with special reference to the intensity of the conditioning regimen.

Second, the characteristics of patients with MS varied across studies: older studies included almost exclusively patients with SPMS, a disease stage with higher probability to continue progressing after transplant.[14] The proportion of patients with RRMS increased over time and some recent studies[17,18] only included patients with RRMS.

Third, due to the well-known drawbacks of EDSS as a measure of progression, its poor reproducibility,[24] and its low interrater agreement,[25] it is difficult to compare and pool EDSS progression when measured in different contexts.

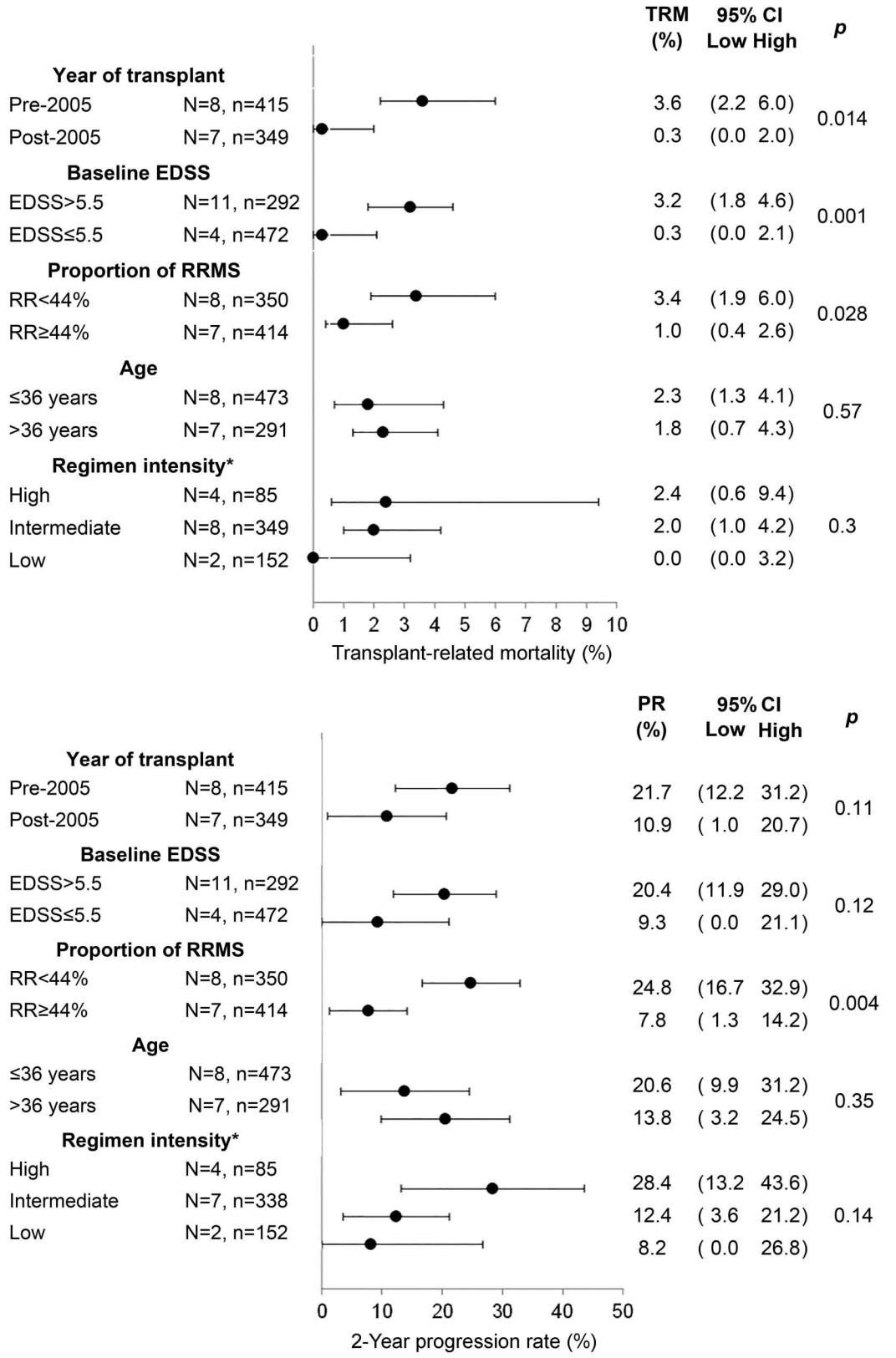
As a likely consequence of these heterogeneities, the progression rates during follow-up are variable among studies. The effect of the disease stage emerged in this meta-analysis as a factor affecting the progression rates after transplant, while the regimen intensity did not. The failure to detect a clear effect on progression of the regimen strategy can probably be imputed to multiple reasons, such as low numbers, different patient populations treated, and different regimens used.

Another limitation of this analysis is that some factors are likely covarying: most of the patients who were included in the earlier studies had progressive disease with relatively advanced disability. However, a formal analysis of covariance is not possible with this study level meta-analysis; therefore, this analysis cannot formally address whether the stage of the disease, the level of disability, or the year of transplant were independent factors associated with TRM and progression.

It is difficult to compare outcomes of aHSCT with those reported in clinical trials of drugs for MS, since the population eligible to receive aHSCT generally has much more aggressive or advanced forms/stages of MS than the ones enrolled in clinical trials. Patients included in clinical trials that resulted in a drug registration all had RRMS, while the majority of studies of aHSCT include mostly patients with SPMS (10 out of 15), with an average median proportion of patients with SPMS of 56%; the median EDSS at enrollment for most of the studies pooled in this analysis is higher than 6, while patients included in clinical trials have EDSS = 6 as their upper limit to be included. Therefore, a rate of progression of 17% after 2 years from transplant can hardly be judged against the rates obtained in clinical trials: it is generally higher than the rate obtained in treated arms of trials in RRMS (e.g., the rate of progression after 2 years was 13% in patients treated with alemtuzumab but it was 20% in patients treated with interferon [IFN]–β-1a in the Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis, Study Two [CARE-MS II] study[26]); on the other hand, it is much lower than the rate of progression in trials in SPMS (e.g., the rate of progression after 2 years was around 45% in patients treated with IFN-β-1a or placebo in the Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-β-1a in MS [SPECTRIMS] study[27]).

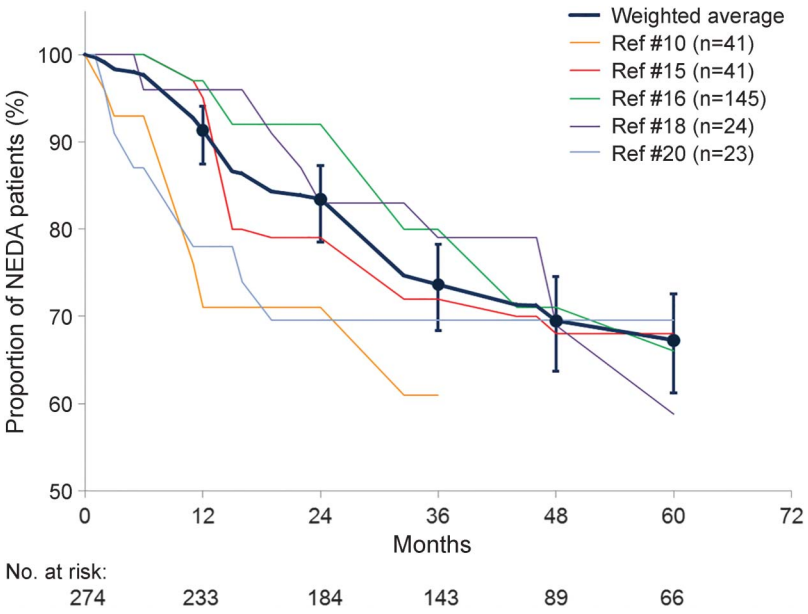
On the other hand, as highlighted in a recently published article by Atkins et al.[20], the largest contribution to disease activity events in transplanted

Figure 3 Forest plot



Forest plot for the meta-regression to assess transplant-related mortality (TRM, defined as the number of deaths occurring within 100 days from transplant divided by the number of transplanted patients) and 2 years progression rate (PR) in different subgroups defined according to baseline characteristics and transplant procedures. *Two studies were excluded since they had different regimens. CI = confidence interval; EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis.

Figure 4 Proportion of patients with no evidence of disease activity (NEDA) over time in single studies and as a pooled estimate



patients comes from disability progression, rather than relapses or MRI activity, similar to what is typically observed in patients with RRMS treated with DMT. In their study, Atkins et al.[20] detected a disappearance of relapse and MRI activity after aHSCT up to 6 years after the procedure. This observation is confirmed by the very high proportion of NEDA patients over time that was estimated by pooling the studies reporting this information during follow-up: patients with NEDA were 83% after 2 years and 67% after 5 years, proportions much higher than those reported for all the most efficacious drugs in published clinical trials.[28] This reinforces the recently reported results[29] comparing the proportion of NEDA in 2 aHSCT studies with that achieved by all the other drugs.

The risk of TRM is the other side of the coin and it represents one of the reasons why the neurologic community is reluctant to consider this therapy, perceiving this risk as unacceptably high. In this meta-analysis, the TRM, defined according to the hematologists' definition as mortality within 100 days from transplant, was 2.1%, and there was no additional mortality during the first year after transplant. In the aHSCT setting, a clinically relevant hematopoietic and immunologic recovery is generally completed within the first 6 months and therefore no adverse events are expected beyond this timeframe, as opposite to the allogeneic setting, where chronic graft-versus-host disease may result in adverse events also in the intermediate or long term. However, this overall rate of death must be looked at more carefully; in fact, subgroup analysis shows that TRM is close to zero in studies including patients who were younger, with RRMS rather than SPMS, with a lower baseline EDSS, and performed in more recent years, suggesting that patient selection and transplant care may significantly influence mortality. Moreover, in the last update of the EBMT Registry, just 1 death was recorded out of 232 procedures in patients with MS reported to the EBMT Registry after 2012 (Dr. Saccardi, personal communication, 2016).

In this meta-analysis, we demonstrate significant association of phase/form of disease (RRMS) with lower progression rate and treatment-related mortality. NEDA rates favorably compare with those reported for DMTs and suggest that aHSCT could be considered as a potentially more effective alternative in selected patients.

To gain a clear understanding of the role of aHSCT for treatment of patients with inflammatory active forms of MS, a comparative trial is needed. Experts' consensus was reached on the design of a phase 3 trial aimed at testing the effectiveness and safety of aHSCT vs current (natalizumab, alemtuzumab) and future (e.g., potentially ocrelizumab) approved high-efficacy DMT.[30]

AUTHOR CONTRIBUTIONS

M.P.S. had the idea for the analysis, contributed to data extraction, performed all the statistical analyses, and wrote the article. P.M. contributed to the studies selection, critically revised all the analyses, and largely contributed to writing the article. I.S. collected and extracted all the data, participated in data analysis, and contributed to article drafting. A.S. collected and extracted all the data, participated in specific sections of statistical analysis, and contributed to article drafting. A.L. helped in data collection and extraction, drafted the tables, and contributed to article drafting. R.S. participated in classification of articles according to transplant characteristics and wrote the section on hematologic issues. G.L.M. helped in selecting the studies and the patients to be included avoiding overlaps and largely contributed to writing the article.

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DISCLOSURE

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Editor's Choice

Editors' Note: In response to the article "Hand postures in primary and secondary generalized tonic-clonic seizures," Dr. Mintzer explains why the statistical methodology employed by the authors, Fisher exact test with Bonferroni correction for multiple comparisons, was not ideal and that the version for multiple groups would have been preferable. He also reinforces a point brought up in a previous comment by Dr. Lanska: multiple events from the same patient should not be considered independent for the purpose of statistical analysis. Authors Siegel and Tatum describe how they addressed the problem statistically. Authors Uruha et al. report that the myxovirus resistance A (MxA) polyclonal antibodies used in their study, "Sarcoplasmic MxA expression: A valuable marker of dermatomyositis," have been discontinued by the company that produced them. The authors describe the results of their tests into the company's monoclonal antibody alternative, concluding that the alternative can be used comparably to the original, but may require higher concentrations.

—Megan Alcauskas, MD, and Robert C. Griggs, MD

LETTER RE: HAND POSTURES IN PRIMARY AND SECONDARY GENERALIZED TONIC-CLONIC SEIZURES

Scott Mintzer, Philadelphia: I congratulate Drs. Siegel and Tatum[1] for the novel examination of hand postures in different seizure types. However, I have concerns that the statistical analysis was not done properly.

The authors reported the use of Fisher exact test with Bonferroni correction for multiple comparisons.[1] Fisher exact test is most often used to analyze 2 × 2 contingency tables. There is a version for multiple groups, but it does not appear that it was used, as it would require the use of posttests and none were mentioned. The use of 3 sets of pairwise comparisons to compare 3 different groups violates the test assumptions. A more appropriate statistical practice is to use a test designed to compare multiple groups, followed by pairwise posttests if there is significance in the main test.

In addition, the concern raised by Dr. Lanska[2] in a previous comment on this article was not adequately addressed by the authors.[3] While the events may be considered independent from a clinical diagnostic standpoint, that does not make them independent from a statistical analysis standpoint. After all, it is the nature of the disease that seizures are stereotyped within a given patient.

Owing to these concerns, the *p* values reported by the authors may provide an inaccurate picture of statistical significance. The data should be reanalyzed.

1. Siegel J, Tatum WO. Hand postures in primary and secondary generalized tonic-clonic seizures. Neurology 2016; 87:1802–1805.
2. Lanska DJ. Electronic response to Siegel and Tatum: Hand postures in primary and secondary generalized tonic-clonic seizures. Neurology 2016. Available at: neurology.org/content/87/17/1802/reply#neurology_el;65459. Accessed January 18, 2017.
3. Siegel JL. Author response to Dr. Lanska [Electronic response to Siegel and Tatum: Hand postures in primary and secondary generalized tonic-clonic seizures]. Neurology 2016. Available at: neurology.org/content/87/17/1802/reply#neurology_el;65459. Accessed January 18, 2017.

AUTHOR RESPONSE: HAND POSTURES IN PRIMARY AND SECONDARY GENERALIZED TONIC-CLONIC SEIZURES

Jason Siegel, William O. Tatum, Jacksonville, FL: We thank Dr. Mintzer for the interest in our article[1] and for the comments on the statistical significance of our findings in response to our prior comment to Dr. Lanska.[2,3]

We agree that more complex 3-way statistics could be initially performed on the overall data; nevertheless, our statistical analysis used the pairwise approach to directly address the comparisons of greatest interest to us.

We appreciate the distinction pointed out between clinical and statistical independence to highlight the difference between them. To this point, we also used generalized estimating equation models to account for the potential correlation among variable independent seizures from different individual patients. The results using this metric were similar to our published results and served to validate the accuracy of our findings. Future prospective assessment analyzing 3 independent arms to study epilepsies and nonepileptic events may further validate our initial clinical findings.

1. Siegel J, Tatum WO. Hand postures in primary and secondary generalized tonic-clonic seizures. Neurology 2016; 87:1802–1805.
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AUTHOR UPDATE: SARCOPLASMIC MXA EXPRESSION: A VALUABLE MARKER OF DERMATOMYOSITIS

Akinori Uruha, Shigeaki Suzuki, Ichizo Nishino, Tokyo: Soon after our article published,[1] we learned the sale of the myxovirus resistance A (MxA) polyclonal antibodies used in the study (Mx1/2/3 [H-285], sc-50509, Santa Cruz Biotechnology, Dallas, TX) had been discontinued. Furthermore, we received inquiries from several physicians concerning alternate MxA antibodies. We tested the company's monoclonal antibody alternate (Mx1/2/3 [C-1], sc-166412) on frozen muscle sections at various dilutions in 2% bovine serum albumin in PBS using the Ventana immunohistochemistry detection system (Ventana Medical Systems, Tucson, AZ) with or without the enhancement mode. Muscle samples tested included MxA-positive dermatomyositis (n = 3, including 1 juvenile participant), MxA-negative dermatomyositis (n = 3), anti-Jo-1 myopathy (n = 3, MxA-negative), and immune-mediated necrotizing myopathy (n = 3, comprising 1 with anti-signal recognition particle antibodies [MxA-negative], 1 with anti-3-hydroxy-3-methylglutaryl-CoA reductase antibodies [MxA-negative], and 1 without those antibodies [MxA-positive]). We observed essentially the same staining pattern at comparable signal intensity as the original polyclonal antibodies at 1:10 dilution with the enhancement mode although the signal was barely detected at the manufacturer's recommended dilution (starting dilution: 1:50), indicating that the monoclonal antibody alternate can be similarly used to detect sarcoplasmic MxA expression on frozen muscle sections for the diagnosis of dermatomyositis (although higher concentration is necessary).

1. Uruha A, Nishikawa A, Tsuburaya RS, et al. Sarcoplasmic MxA expression: a valuable marker of dermatomyositis. Neurology 2017;88:493–500.

CORRECTIONS

Revisiting neurofibromatosis type 2 diagnostic criteria to exclude LZTR1-related schwannomatosis

In the article "Revisiting neurofibromatosis type 2 diagnostic criteria to exclude LZTR1-related schwannomatosis" by M.J. Smith et al.,[1] there are errors in table 4. Row 3 should have read "FDR Family history of NF2 OR unilateral VS AND two of[b]: meningioma, cataract, glioma, neurofibroma, nonvestibular schwannoma, cerebral calcification (if UVS + ≥2 nonintradermal schwannomas need negative LZTR1 test) OR." Row 4 should have read: "Multiple meningioma (2 or more) AND unilateral VS OR two of: Cataract, glioma, neurofibroma, nonvestibular schwannoma, cerebral calcification OR." The authors regret the errors.

REFERENCE

1. Smith MG, Bowers NL, Bulman M, et al. Revisiting neurofibromatosis type 2 diagnostic criteria to exclude LZTR1-related schwannomatosis. Neurology 2017;88:87–92.

Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis

In the article "Autologous hematopoietic stem cell transplantation in multiple sclerosis: A meta-analysis" by M.P. Sormani et al.,[1] there is an error in figure 2. The label at the top of the right panel should have read "5-Year progression rate (%)" rather than "2-Year progression rate (%)" as originally published. The editorial staff regrets the error.

REFERENCE

1. Sormani MP, Muraro PA, Schiavetti I, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a meta-analysis. Neurology 2017;88:2115–2122.

Author disclosures are available upon request (journal@neurology.org).