Original article

Autologous hematopoietic stem cell transplantation is superior to alemtuzumab in patients with highly active relapsing multiple sclerosis and severe disability

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A B S T R A C T

Objective: To assess the differences of treatment outcomes regarding disease activity in patients with highly active relapsing multiple sclerosis (RMS), treated with autologous hematopoietic stem cell transplantation (HSCT) or alemtuzumab (ATZ).

Methods: Open-label prospective single-center observational cohort study, enrolling patients with highly active RMS for treatment with ATZ or HSCT between 2014 and 2021.

Results: A total of 50 patients (31/50 (62 %) in HSCT vs 19/50 (38 %) in ATZ group) were included. There were no significant differences in relapse rate, MRI activity or disability worsening between the two study groups during the first two years after treatment onset. However, at 3 to 5 years follow-up, HSCT was superior to ATZ in all the aforementioned aspects. Kaplan-Meier analysis at 5 years post treatment revealed superiority of HSCT in relapse rate (69.6 % vs 95.7 %, $p = 0.027$), MRI activity (54.5 % vs 75.1 %, $p = 0.038$) and disability worsening (57.1 % vs 90.9 %, $p = 0.031$).

Conclusions: ATZ may halt disability progression early in the course of highly active RMS, but the disability starts accumulating later, while in HSCT patients disability improvement is consistent both 3 and 5 years after treatment onset.

1. Introduction

Multiple sclerosis (MS) is a chronic, lifelong disabling disease of the central nervous system with unpredictable outcomes. Highly active relapsing multiple sclerosis (RMS) develops in up to 15 % of MS patients despite the use of disease-modifying therapies (DMTs) (Díaz et al., 2019) and is characterized by frequent, severe relapses, incomplete recovery after relapses, rapidly accumulating, permanent disability, and high magnetic resonance imaging (MRI) activity, usually requiring aggressive treatment strategies to maintain disease stability (Correale et al., 2023).

Alemtuzumab (ATZ) and autologous hematopoietic stem cell transplantation (HSCT), could be considered the strongest and most appropriate therapies for patients with highly active RMS due to their immediate immune reconstitution effects (Sorensen and Sellebjerg, 2019; Karussis and Petrou, 2018; Cencioni et al., 2022). ATZ is currently considered as one of the most highly effective DMTs available for RMS that results in durable efficacy in the absence of continuous treatment (Havrdova et al., 2017, Holmøy et al., 2019). In the comprehensive

systematic analysis of all available DMTs, made on the behalf of the American Academy of Neurology, ATZ came out on top for prevention of relapses as well as disability progression (Rae-Grant et al., 2018). Long-term clinical trials of ATZ reported rates of "no evidence of disease activity" (NEDA) as high as 60–75 % per year, with 34 % of patients maintaining NEDA during the 12-year follow-up period (Steingo et al., 2020).

On the other hand, immunosuppression followed by a HSCT can be considered as an alternative therapeutic option for patients with highly active RMS experiencing disease activity despite the use of highly active DMTs, including ATZ. In the past years, HSCT has been demonstrated to be the highly efficacious, relatively safe therapeutic option due to careful patient selection and technical advances in transplant centers (Muraro et al., 2017, Alexander et al., 2018). Studies have shown the potential to maintain a much higher proportion of NEDA patients at 2 years (ranging from 78 % to 83 %) and 5 years (ranging from 60 % to 68 %) after HSCT comparing to DMTs in MS patients (Sormani et al., 2017). Unfortunately, there is a lack of studies directly comparing HSCT

with approved highly effective DMTs in MS. Only one randomized clinical trial has shown higher efficacy of HSCT versus DMTs resulting in prolonged time to disease progression in RMS patients (Burt et al., 2019). However, this trial did not include highly active DMTs like alemtuzumab or ocrelizumab. Furthermore, the patient population in this trial differed from real-world MS patients in several aspects.

Three real-world treatment experiences with HSCT and ATZ were published in the recent years (Boffa et al., 2020, Zhukovsky et al., 2021, Häußler et al., 2021). All the studies have demonstrated the superiority of HSCT in maintaining NEDA (Boffa et al., 2020, Zhukovsky et al., 2021, Häußler et al., 2021). However, the trials included relatively small population groups (Boffa et al., 2020, Häußler et al., 2021), relatively short follow-up period (Zhukovsky et al., 2021) and heterogenous groups: patients with different disease courses (Häußler et al., 2021), patients without disease activity in the last 12 months (without relapses and/or activity on MRI) (Boffa et al., 2020, Häußler et al., 2021) or unbalanced patients at the baseline evaluation in terms of age and EDSS score (Boffa et al., 2020).

Further researches are needed to compare HSCT with other high efficacy DMTs and to assess long-term outcomes and safety in the real-world MS patients. Experiences from single centers and sustained follow-up of treated MS patients provide important information about the efficacy and safety of HSCT.

This single-center real-world study aimed at determining the differences of treatment outcomes in patients suffering from severe disability due to highly active RMS, after treatment with HSCT or ATZ.

2. Methods

2.1. Study design

This open-label prospective single-center observational cohort study was performed at Vilnius University Hospital Santaros Klinikos, Lithuania. Fifty patients, treated with ATZ or HSCT between 2014 and 2021, were enrolled in the study. All participants signed the Informed Consent Form for collection of the data and its use for research purposes. Treatment decisions were based on the clinical and radiological judgment of the neurology team. Patients were considered eligible for HSCT or ATZ treatment if they had clinically definite highly active RMS with high disease activity, defined as at least one severe attack under previous DMTs in the last year and new T2 or active MRI lesions or at least two severe attacks without new changes on MRI. High efficacy therapies for MS were fingolimod, cladribine, natalizumab and ocrelizumab. These high efficacy therapies are based on the regulations of the Ministry of Health in Lithuania.

Exclusion criteria were primary or secondary progressive MS; neurological disorders, other than MS; active infections; pregnancy; pulmonary, cardiac, renal, or liver dysfunction; abnormal blood cell counts. The HSCT procedure was carried out at Hematology, Oncology and Transfusion Medicine Center of Vilnius University Hospital Santaros Klinikos, Vilnius, Lithuania. ATZ infusions were performed at Neurology Department of Vilnius University Hospital Santaros Klinikos.

2.2. Primary and secondary endpoints

The primary endpoint of the study was the proportion of patients achieving NEDA in Years 1, 2, 3, 4 and 5 after the treatment. NEDA was defined as the absence of disease relapses, disability progression and MRI activity. PIRA was defined as disability accumulation in the EDSS scale at 6 months during a period free from relapses. MS relapses were diagnosed by the examining neurologist and were defined as neurological symptoms lasting more than 24 h, occurring at least 30 days after the onset of a preceding relapse and not associated with any other trigger. Disability progression or disability improvement was defined as confirmed yearly EDSS increase or decrease by at least 1 point when baseline EDSS was ≤ 5.0, and 0.5 points when baseline EDSS was ≥ 5.5.

MRI activity was defined as new, enlarging, or Gd-enhancing lesions.

Information about relapses in six months, one and two years before HSCT was collected from the National Multiple Sclerosis Registry. Neurological assessment was performed by the same neurologist and MRI was assessed by the same radiologist. All MRI imaging was performed using the same - 3.0 Tesla scanner Philips ACHIEVA 3TX.

2.3. Treatment

HSCT was performed in line with the 2012 guidelines of the European Society for Blood and Marrow Transplantation (EBMT) wirh reference to the Autologous Hematopoietic Stem Cell Transplantation Trial in MS (ASTIMS) protocol (Snowden et al., 2012). Peripheral blood stem cells mobilization was performed with cyclophosphamide (2 g/m^2 single dose with intravenous mesna prophylaxis). Subcutaneous filgrastim 10 μg/kg was started on day +7 and peripheral blood stem cell (PBSC) apheresis procedure was targeted on day +12 after cyclophosphamide infusion. Collected cells were cryopreserved and stored. The conditioning regimen was intravenous cyclophosphamide 200 mg/m^2 and rabbit antithymocyte globulin 6,5 mg/kg. Prophylaxis for bacterial, viral and fungal infection was administered during neutropenia. Prophylaxis for herpes viruses and *Pneumocystis jirovecii* was continued for a minimum of three months.

ATZ was administered in accordance with the indications of the SPC (Lemtrada product information. European Medicines Agency, 2023): as two scheduled annual courses, consisting of 12 mg/day infusion of ATZ on 5 consecutive days at baseline and on 3 consecutive days 12 months later, with each daily infusion lasting 4 hours. Premedication treatment included methylprednisolone, paracetamol and clemastine. From the first day of treatment, all patients used prophylaxis with acyclovir (400 mg per day for 1 month). To reduce the risk of listeria infection, diet recommendations were given for all patients (one month prior to, during, and at least for one month after ATZ infusion).

2.4. Statistical analyses

Data were analyzed using statistical software package SPSS (version 25 for Windows). Continuous variables were reported as medians and ranges or means and standard deviations. To determine statistically significant differences between two groups, the χ^2 test, Student's t test and Mann-Whitney tests were used. Survival was estimated using Kaplan-Meier plots (95 % CI). A significance level $p < 0.05$ was accepted.

3. Results

3.1. Baseline characteristics of the study population

A total of 50 patients (31/50 (62 %) in the stem cell transplantation group (HSCT) vs 19/50 (38 %) in the Alemtuzumab (ATZ) group) were included in the final analysis. Baseline demographics did not differ between the two groups (13/19 (68.2 %) females in ATZ vs 22/31 (70.2 %) in HSCT group, $p = 1.00$; median age 35 (IQR 28-39) in ATZ vs 38 (IQR 33-42) $p = 0.36$ in HSCT group). However, HSCT patients were more disabled at baseline (baseline EDSS median 6.0 (5.5–6.0) for HSCT vs 4.5 (4.0-5.5) for ATZ, $p = 0.01$, respectively) and had been pretreated with high efficacy DMTs more frequently compared to ATZ patients (18/31 (58.1 %) vs 4/19 (21.1 %), $p = 0.003$, respectively). Baseline characteristics of the two study groups are summarized in Table 1.

3.2. Primary end-point analysis

Detailed post-treatment analytes are shown in Table 2. HSCT and ATZ group patients were compared yearly. Median follow-up did not differ between the two groups (52 months (IQR 36-63) in HSCT vs 59 months (IQR 36-70) in ATZ group, $p = 0.47$).

Table 1

Pretreatment characteristics of the cohort.

	Alemtuzumab (ATZ) N19	HSCT N31	P value
Age, years, median (IQR)	35 (28-39)	38 (33-42)	0.360
Female, N (%)	13 (68.4)	22 (70.9)	1.00
Last known DMT			
High efficacy therapies, N (%)	12 (63.1)	30 (96.7)	**0.003**
Platform therapies, N (%)	7 (36.8)	1 (3.3)	**0.003**
Number of past DMT's, median (IQR)	2 (2-3)	2 (2-3)	0.416
Baseline EDSS, median (IQR)	4.5 (4.0-5.5)	6.0 (5.5-6.0)	**0.01**
Number of relapses before ATZ/ HSCT, median (IQR)	2 (2-3)	3 (2-4)	0.067
Disease duration, years	8.2 ± 5.5	8.3 ± 4.9	0.975

ATZ – alemtuzumab, HSCT – haematopoietic stem cell transplantation, DMT's-disease modifying therapies; EDSS- Expanded Disability Status Scale;

Table 2

Post-treatment characteristics.

	Alemtuzumab (ATZ) N19	HSCT N31	P value
Total number of relapses, median (IQR)	1 (0-3)	0 (0-1)	**0.035**
ARR, median (IQR)	0.0282 (0-0.05)	0 (0-0.02)	**0.035**
Median EDSS (IQR)			
Year 1 (ATZ N19, HSCT N31)	4.0 (3.0-5.5)	5.5 (4.0-6.0)	0.426
Year 2 (ATZ N18, HSCT N29)	4.0 (3.0-5.5)	6.0 (4.0-6.0)	0.352
Year 3 (ATZ N16, HSCT N24)	4.5 (3.0-5.5)	6.0 (4.0-6.0)	0.318
Year 4 (ATZ N14, HSCT N18)	5.0 (3.0-6.0)	6.0 (4.0-6.0)	0.812
Year 5 (ATZ N12, HSCT N11)	5.25 (3.5-6.0)	6.0 (4.0-6.0)	0.621
Change in EDSS from baseline, median (IQR)	-0.12 (0.0-0.0)	-0.72 (-2.0-0.0)	**0.002**
Year 1 (ATZ N19, HSCT N31)	-0.08 (0.0-0.375)	-0.64 (-2.0-0.0)	**0.008**
Year 2 (ATZ N18, HSCT N29)	0 (0.0-0.5)	-0.6 (-2.0-0.0)	**0.019**
Year 3 (ATZ N16, HSCT N24)	+0.29 (0.0-0.5)	-0.5 (-2.0-0.5)	**0.009**
Year 4 (ATZ N14, HSCT N18)	+0.38 (0.0-0.88)	-0.5 (-2.0-0.5)	0.075
Year 5 (ATZ N12, HSCT N11)			
NEDA-3 (%)			
Year 1 (ATZ N19, HSCT N31)	52	80	**0.05**
Year 2 (ATZ N18, HSCT N29)	44	79	**0.027**
Year 3 (ATZ N16, HSCT N24)	56.2	75	0.305
Year 4 (ATZ N14, HSCT N18)	57.2	72	0.465
Year 5 (ATZ N12, HSCT N11)	25	54.5	0.414
PIRA (%)			
Year 1 (ATZ N19, HSCT N31)	5.3	3.2	0.620
Year 2 (ATZ N18, HSCT N29)	10.5	6.5	0.498
Year 3 (ATZ N16, HSCT N24)	10.5	3.2	0.348
Year 4 (ATZ N14, HSCT N18)	5.3	9.7	0.403
Year 5 (ATZ N12, HSCT N11)	0	3.2	0.478
Median (IQR) follow-up, months	59 (36-70)	52 (36-63)	0.47

HSCT – haematopoietic stem cell transplantation, ARR- annualized relapse rate; EDSS- Expanded Disability Status Scale; NEDA-3- No evidence of disease activity; PIRA- progression independent of relapse activity;

Fewer relapses were seen in the HSCT group compared to ATZ (median annual relapse rate (ARR) 0 (IQR 0-0.02) vs 0.0282 (IQR 0–0.05), $p = 0.035$, respectively).There were no differences in yearly median EDSS scores between the two groups, however, when compared to baseline EDSS, HSCT group showed gradual yearly improvement in EDSS scores, while ATZ group experienced disease worsening from year 3 onwards (Table 2).

NEDA-3 estimates were significantly lower in ATZ compared with HSCT at year 2 from baseline (44 % vs 79 %, $p = 0.027$, respectively), but did not reach statistical significance beyond year 2. Pooled Kaplan-Meier estimates were non-discriminative (supplementary Fig. 1).

Progression independent of relapse activity (PIRA) was low in both groups without statistically significant differences (range 0 %-10.5 % in ATZ and 3.2–9.7 % in HSCT groups, depending on the year of follow-up, Table 2).

3.3. Sub-analysis of treatment efficacy by yearly intervals

In the primary early comparison of treatment efficacy between ATZ and HSCT we observed gradual improvements of EDSS scores in HSCT group, and, on the contrary, gradual disability accumulation in ATZ patients onward from year 3 of follow-up. However, despite these observations, efficacy estimates beyond year 3 were non discriminative, primarily due to decreasing number of patients in follow-up further from baseline. For this reason, we conducted an interval-based analysis with a cut-off at year 3. In the final analysis, ATZ and HSCT efficacy estimates were compared separately between two intervals: maximum 2 years of follow-up and beyond 3 years of follow-up.

Detailed analysis of the study groups is shown in Table 3. There were no significant differences in relapse rate (10/19 (52.7 %) in ATZ vs 9/31 (29.1 %) in HSCT group, $p = 0.209$), MRI activity (5/19 (26.3 %) in ATZ vs 3/31 (9.7 %) in HSCT group, $p = 0.223$) or disability worsening (6/19 (31.5 %) in ATZ vs 3/31 (9.7 %) in HSCT group, $p = 0.12$) between the two study groups during the first two years after treatment onset. However, 3 years after follow-up and beyond, HSCT was superior to ATZ in all the aforementioned aspects (see Table 3). Additionally, in the HSCT group, improvements in EDSS scores were seen during the first two years and scores continued to improve beyond 3 years of follow-up (EDSS decreased during years 1-2 in 3/19 (15.7 %) of ATZ vs 20/31 (64.5 %) of HSCT group patients, $p = 0.005$; EDSS decreased during years 3-5 in 3/16 (18.8 %) of ATZ vs 14/24 (58.3 %) of HSCT group, $p = 0.022$))

Kaplan-Meier estimates between ATZ and HSCT groups for freedom of MRI activity, freedom of relapses and freedom of disease worsening are displayed in Fig. 1. HSCT was superior to ATZ in all aspects at 5 year time point: 69.6 % vs 95.7 %, $p = 0.027$; 54.5 % vs 75.1 %, $p = 0.038$; 57.1 % vs 90.9 %, $p = 0.031$, respectively.

Table 3

Subanalysis by year intervals after treatment.

	Years 1-2 after treatment			Years 3-5 after treatment		
	ATZ N 19	HSCT N 31	P value	ATZ N16	HSCT N24	P value
Relapsed N (%)	10 (52.7)	9 (29.1)	0.209	12 (75)	8 (33.3)	**0.02**
MRI activity N (%)	5 (26.3)	3 (9.7)	0.223	7 (43.5)	1 (4.2)	**0.004**
CDW N (%)	6 (31.5)	3 (9.7)	0.12	8 (50)	4 (16.7)	**0.037**
Improved EDSS, N (%)	3 (15.7)	20 (64.5)	**0.005**	3 (18.8)	14 (58.3)	**0.022**
NEDA-3 (%)	15.7	45.2	**0.03**	0	50	**0.001**

ATZ – alemtuzumab, HSCT – haematopoietic stem cell transplantation, CDW-confirmed disability worsening; EDSS- Expanded Disability Status Scale; MRI-magnetic resonance imaging; NEDA-3- No evidence of disease activity;
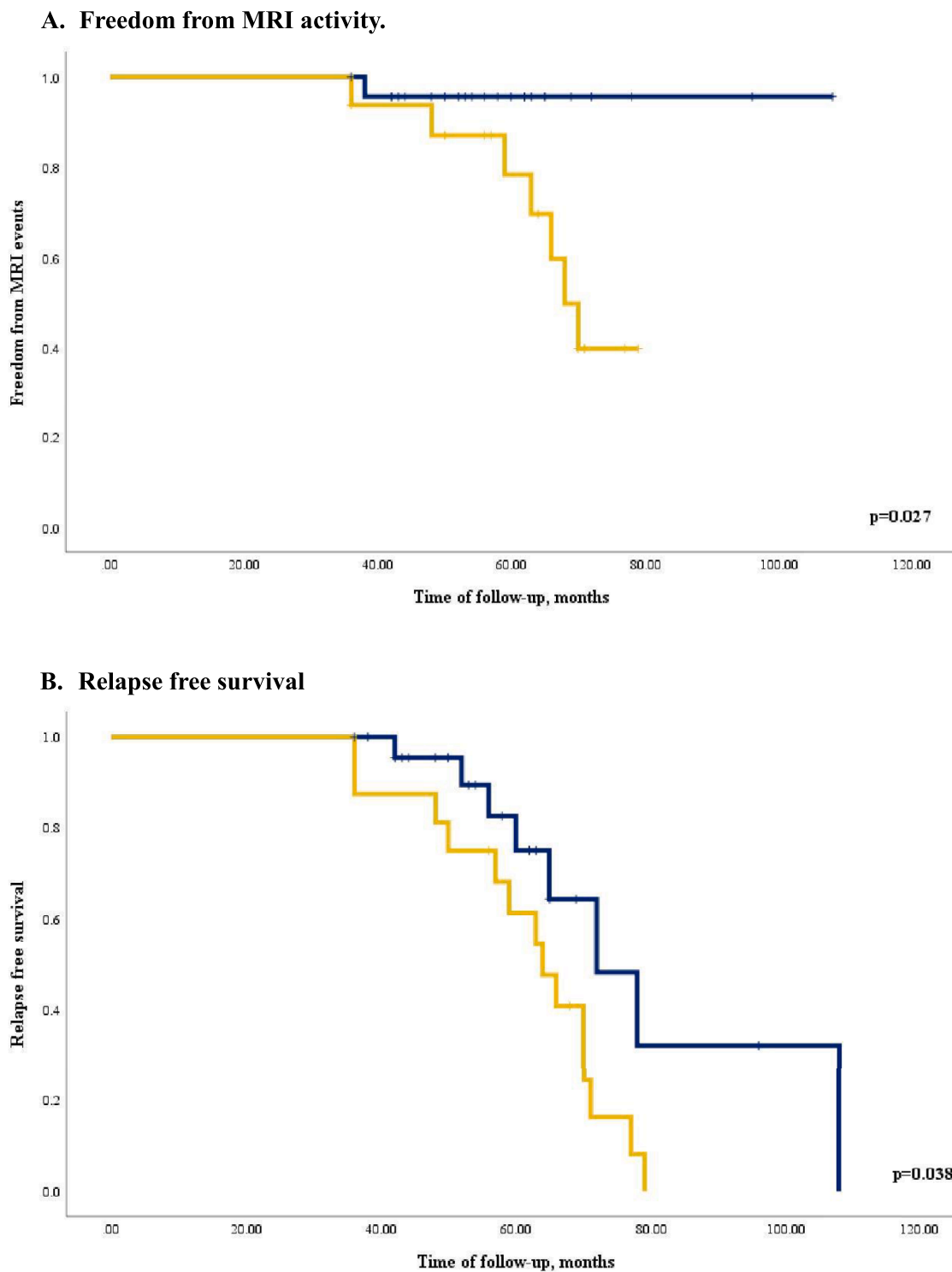
A. Freedom from MRI activity.

B. Relapse free survival

Fig. 1. Kaplan-Meier estimates of ALT vs HSCT. HSCT is depicted in blue.

4. Discussion

The present study compares outcomes of RMS treatment by HSCT or ATZ at a single tertiary MS center. Although previous reports have described both safety, efficacy of HSCT in RMS patients and compared it with ATZ in the aforementioned aspects (Boffa et al., 2020, Zhukovsky et al., 2021, Häußler et al., 2021), additional points from our data with potential clinical implications are worth highlighting.

Firstly, the present data indicate that HSCT remains beneficial beyond three years after treatment onset. Earlier reports suggest superiority of HSCT in relapse rate, MRI activity and disability progression over ATZ (Zhukovsky et al., 2021, Häußler et al., 2021) at three years follow-up. In contrast to these findings, we have observed that HSCT retains superiority over ATZ beyond year 3 after treatment initiation. Importantly, our data indicate that HSCT not only halts disability worsening but might also improve disability measures. That is in

C. Freedom from disease worsening.
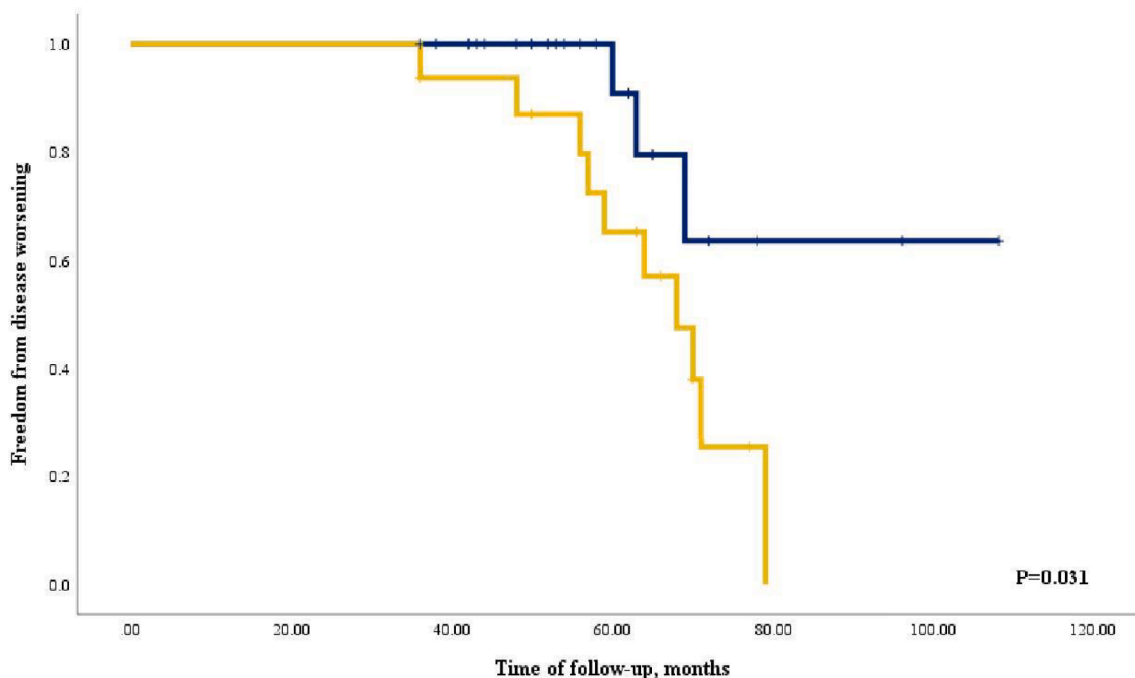
D. EDSS improvement
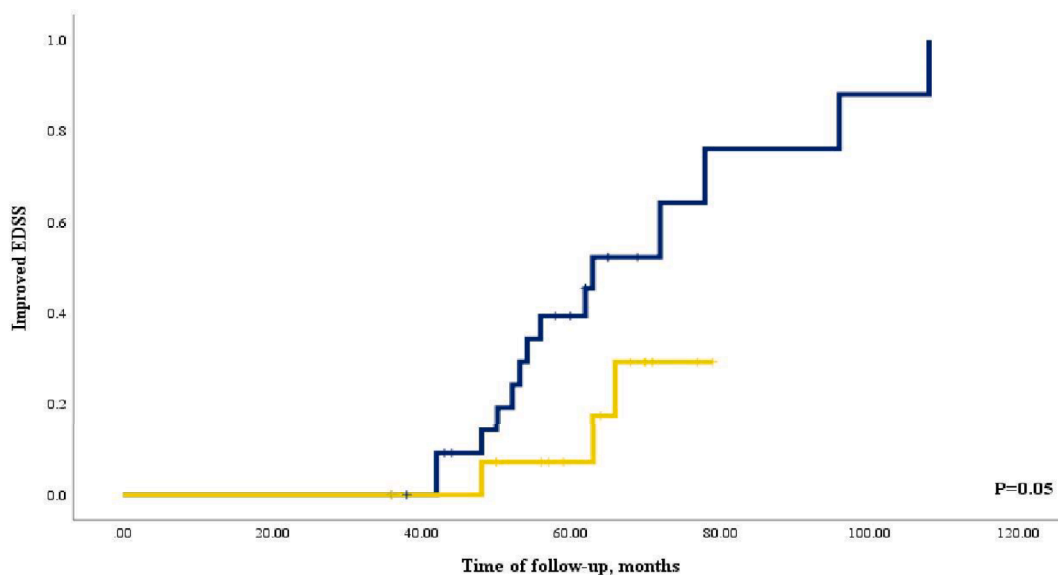
At 5 years, 50% have improvements in EDSS scores in HSCT compared to 10 % in ALT.

Fig. 1. (*continued*).

contrast to ATZ's real-world and clinical trial data where the rate of disability stabilization, but not improvement, is achieved in most cases. However, disability worsening remains low in both ATZ and HSCT groups (Coles et al., 2012, Havrdova et al., 2017, Russo et al., 2022).

Secondly, with regards to disease worsening, studies on Ocrelizumab and Natalizumab reported rates of disease worsening not associated with relapses (PIRA) between 70 and 80 % (Kappos et al., 2018, Kappos et al., 2020). It is in line with real-world data where a quarter of patients continues to accumulate disability independently of relapses (Graf et al., 2021). This suggests that some high efficacy DMTs are good for controlling active inflammation (relapses and MRI lesions), but not

secondary disease progression. On the other hand, PIRA is consistently less than 10 % in our series, regardless of disease duration and treatment modality. Along with reports, suggesting superiority of highly-efficacious treatments over platform therapies at MS onset for disability progression (Spelman et al., 2021) and low rates of conversion from RMS to SPMS in patients on ATZ (Horakova et al., 2020), HSCT may offer additional benefits in early active RMS akin to its better efficacy profile. However, in contrast to ATZ, where early trials showed no effect on progressive forms of the disease (Coles et al., 2006, Coles et al., 1999), there is accumulating evidence that HSCT halts disability progression in more than 60 % of cases in SPMS (Boffa et al., 2021, Burt

et al., 2022). These data therefore argue the "early treatment window" concept and previous conclusions of early ATZ trials that immunodepleting treatments are not effective in progressive forms of MS due to ongoing neurodegeneration and not inflammation.

Finally, with regards to the early "treatment window", major differences between ATZ and HSCT are present. As demonstrated previously, for halting disability progression, ATZ is administered early in the disease course and in persons with minor functional disability (Coles et al., 2012, Havrdova et al., 2017, Russo et al., 2022). In contrast, HSCT might offer a broader "treatment window" with beneficial effects on disease progression and disability reversal in persons with both active and progressive forms of disease and a variable degree of accumulated disability as shown in the present and past series (Giedraitiene et al., 2020, Murrieta-Alvarez et al., 2021). Although it is currently unreasonable to consider early HSCT therapy for the treatment of MS due to its low availability and variable national policies, this data suggests that HSCT is still superior to ATZ even in patients with severe disability at baseline. Along with the data from the present and other studies, there is grounds for more clinical trials of HSCT on disease stabilization and progression reversal in patients with severe disability.

Limitations of this study include a relatively small sample size and non-randomized study design. However, there are no randomized controlled studies, with the exception of one small trial (Burt et al., 2019), in which a comparative group is used to assess the results of HSCT therapy.

5. Conclusions

ATZ may halt disability progression early in the course of highly active RMS, but disability starts accumulating in later stages after ATZ treatment However, in HSCT patients, disability improvement is consistent at both 3 and 5 years after treatment onset. HSCT is not only superior to ATZ in most efficacy analytes, but might also be beneficial for patients with severe functional disability in disease stabilization and disability improvement. Given these findings, clinical trials evaluating efficacy of HSCT in severe disability in MS patients should be considered.

Author statement

M.V. Conception and design of the study, primary data analysis, drafting of the manuscript; G.F.K. Overall revision for accuracy of the data, tables and Figures, scientific accuracy of the manuscript; R.K. Concept of the study, revision of the manuscript for scientific accuracy; V.T. Data analysis, drafting of the manuscript, revision for scientific accuracy; N.G. conception and design of the study, acquisition of the data, analysis and interpretation of the data, and drafting of the manuscript, revision for scientific accuracy. All of the authors discussed the results and contributed to and approved the final manuscript.

Data availability statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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The authors declare they have no financial interests.

Ethical considerations

The study was approved by the Lithuanian Bioethics Committee in 2011 (2011-01-27 No.: L-12-01/2). Permission to continue the study was granted by the Lithuanian Bioethics Committee in 2018 (2018-02-22 No.: 6B-18-41). All methods were performed in accordance with the relevant guidelines and regulations.

Declaration of Competing Interest

M.V. Conception and design of the study, primary data analysis, drafting of the manuscript; G.F.K. Overall revision for accuracy of the data, tables and Figures, scientific accuracy of the manuscript; R.K. Concept of the study, revision of the manuscript for scientific accuracy; V.T. Data analysis, drafting of the manuscript, revision for scientific accuracy; N.G. conception and design of the study, acquisition of the data, analysis and interpretation of the data, and drafting of the manuscript, revision for scientific accuracy. All of the authors discussed the results and contributed to and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2023.105096.

References

Alexander, T., Farge, D., Badoglio, M., et al., 2018. Hematopoietic stem cell therapy for autoimmune diseases–clinical experience and mechanisms. J. Autoimmun. 92, 35–46.

Boffa, G., Lapucci, C., Sbragia, E., et al., 2020. Aggressive multiple sclerosis: a single-centre, real-world treatment experience with autologous haematopoietic stem cell transplantation and alemtuzumab. Eur. J. Neurol. 27 (10), 2047–2055. Oct.

Boffa, G., Massacesi, L., Inglese, M., et al., 2021. Long-term clinical outcomes of hematopoietic stem cell transplantation in multiple sclerosis. Neurology.

Burt, R.K., Balabanov, R., Burman, J., et al., 2019. Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial. JAMA 321 (2), 165–174.

Burt, R.K., Han, X., Quigley, K., et al., 2022. Real-world application of autologous hematopoietic stem cell transplantation in 507 patients with multiple sclerosis. J. Neurol. 269 (5), 2513–2526.

Cencioni, M.T., Genchi, A., Brittain, G., et al., 2022. Immune reconstitution following autologous hematopoietic stem cell transplantation for multiple sclerosis: a review on behalf of the EBMT autoimmune diseases working party. Front. Immunol. 12, 813957. Feb 1.

Coles, A.J., Wing, M.G., Molyneux, P., et al., 1999. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann. Neurol. 46 (3), 296–304.

Coles, A.J., Cox, A., Le Page, E., et al., 2006. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. J. Neurol. 253 (1), 98–108.

Coles, A.J., Twyman, C.L., Arnold, D.L., et al., 2012. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. Lancet 380 (9856), 1829–1839.

Correale, J., Rush, C.A., Barboza, A., 2023. Are highly active and aggressive multiple sclerosis the same entity? Front. Neurol. 14, 1132170. Mar 3.

Díaz, C., Zarco, L.A., Rivera, DM., 2019. Highly active multiple sclerosis: an update. Mult. Scler. Relat. Disord. 30, 215–224. May.

Giedraitiene, N., Kizlaitiene, R., Peceliunas, V., et al., 2020. Selective cognitive dysfunction and physical disability improvement after autologous hematopoietic stem cell transplantation in highly active multiple sclerosis. Sci. Rep. 10 (1), 21286.

Graf, J., Leussink, V.I., Soncin, G., et al., 2021. Relapse-independent multiple sclerosis progression under natalizumab. Brain Commun. 3 (4), fcab229.

Häußler, V., Ufer, F., Pöttgen, J., et al., 2021. aHSCT is superior to alemtuzumab in maintaining NEDA and improving cognition in multiple sclerosis. Ann. Clin. Transl. Neurol. 8 (6), 1269–1278. Jun.

Havrdova, E., Cohen, J.A., Horakova, D., et al., 2017. Understanding the positive benefit: risk profile of alemtuzumab in relapsing multiple sclerosis: perspectives from the alemtuzumab clinical development program. Ther. Clin. Risk Manag. 13, 1423–1437. Oct 16.

Havrdova, E., Arnold, D.L., Cohen, J.A., et al., 2017. Alemtuzumab CARE-MS I 5-year follow-up: durable efficacy in the absence of continuous MS therapy. Neurology 89 (11), 1107–1116.

Holmøy, T., Fevang, B., Olsen, D.B., et al., 2019. Adverse events with fatal outcome associated with alemtuzumab treatment in multiple sclerosis. BMC Res. Notes 12 (1), 497. Aug 12.

Horakova, D., Boster, A., Bertolotto, A., et al., 2020. Proportion of alemtuzumab-treated patients converting from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis over 6 years. Mult. Scler. J. Exp. Transl. Clin. 6 (4), 2055217320972137.

Kappos, L., Butzkueven, H., Wiendl, H., et al., 2018. Greater sensitivity to multiple sclerosis disability worsening and progression events using a roving versus a fixed reference value in a prospective cohort study. Mult. Scler. 24 (7), 963–973.

Kappos, L., Wolinsky, J.S., Giovannoni, G., et al., 2020. Contribution of relapse-independent progression vs relapse-associated worsening to overall confirmed disability accumulation in typical relapsing multiple sclerosis in a pooled analysis of 2 randomized clinical trials. JAMA Neurol. 77 (9), 1132–1140.

Karussis, D., Petrou, P., 2018. Immune reconstitution therapy (IRT) in multiple sclerosis: the rationale. Immunol. Res. 66 (6), 642–648. Dec.

Lemtrada product information. European Medicines Agency. 2023. https://www.ema.europa.eu/en/documents/product-information/lemtrada-epar-product-information_en.pdf Accessed on 20. September, 2023.

Muraro, P.A., Martin, R., Mancardi, G.L., et al., 2017. Autologous haematopoietic stem cell transplantation for treatment of multiple sclerosis. Nat. Rev. Neurol. 13, 391–405.

Murrieta-Alvarez, I., Cantero-Fortiz, Y., Leon-Pena, A.A., et al., 2021. The 1,000th transplant for multiple sclerosis and other autoimmune disorders at the HSCT-Mexico program: a myriad of experiences and knowledge. Front. Neurol. 12, 647425.

Rae-Grant, A., Day, G.S., Marrie, R.A., et al., 2018. Comprehensive systematic review summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline development, dissemination, and Implementation subcommittee of the American Academy of Neurology. Neurology 90, 789–800.

Russo, C.V., Sacca, F., Frau, J., et al., 2022. A real-world study of alemtuzumab in a cohort of Italian patients. Eur. J. Neurol. 29 (1), 257–266.

Snowden, J.A., Saccardi, R., Allez, M., et al., 2012. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 47, 770–790.

Sorensen, P.S., Sellebjerg, F., 2019. Pulsed immune reconstitution therapy in multiple sclerosis. Ther. Adv. Neurol. Disord. 12, 1756286419836913. Mar 28.

Sormani, M.P., Muraro, P.A., Saccardi, R., et al., 2017. NEDA status in highly active MS can be more easily obtained with autologous hematopoietic stem cell transplantation than other drugs. Mult. Scler. 23 (2), 201–204. Feb.

Spelman, T., Magyari, M., Piehl, F., et al., 2021. Treatment escalation vs immediate initiation of highly effective treatment for patients with relapsing-remitting multiple sclerosis: data from 2 different national strategies. JAMA Neurol. 78 (10), 1197–1204.

Steingo, B., Al Malik, Y., Bass, A.D., et al., 2020. Long-term efficacy and safety of alemtuzumab in patients with RRMS: 12-year follow-up of CAMMS223. J. Neurol. 267 (11), 3343–3353. Nov.

Zhukovsky, C., Sandgren, S., Silfverberg, T., et al., 2021. Autologous haematopoietic stem cell transplantation compared with alemtuzumab for relapsing-remitting multiple sclerosis: an observational study. J. Neurol. Neurosurg. Psychiatry 92 (2), 189–194. Feb.