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Long-term results of autografting persons with multiple sclerosis are better in those not exposed to prior disease-modifying therapies

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ABSTRACT

Introduction: Multiple sclerosis (MS) is a disabling disease that affects young adults. Treatments for MS have increased exponentially in number, efficacy and risk. Autologous hematopoietic stem cell transplantation (aHSCT) can change the natural history of the disease. To analyze if aHSCT should be done early in the course of the disease or after failing of other therapies, we have studied the long-term results of aHSCT in a cohort of persons with MS who were given, or not, immunosuppressive drugs before the transplant.

Materials and methods: Patients with MS referred to our center for aHSCT between June 2015 and January 2023 were prospectively entered in the study. All phenotypes of MS were included (relapsing remitting, primary progressive and secondary progressive). The follow up was assessed with the patient reported EDSS score in an online form; only patients followed by three or more years were included in the analysis. Patients were divided into two groups: Given or not disease modifying treatments (DMT) before the aHSCT.

Results: 1132 subjects were prospectively enrolled. 74 patients were followed for more than 36 months, and the subsequent analysis was done in this cohort. The response rate (RR = improvement + stabilization) at 12, 24 and 36 mo was 84%, 84% and 58% respectively for patients not receiving prior DMT and 72%, 90% and 67% for patients receiving DMT. In the whole group, the EDSS score dropped from a mean of 5.5 to 4.5 at 12 mo, to 5.0 at 24 mo and to 5.5 at 36 mo, after the aHSCT. The EDSS score was on average worsening in patients before the aHSCT, but the transplant stabilized the EDSS score at 3 years in patients with prior exposure to DMT, whereas in persons not given DMT, the transplant resulted in a significant decrease ($p = .01$) of the EDSS score. This indicates a positive response in all patients given aHSCT, but significantly better in those not exposed to DMT before the graft.

Conclusion: The response to aHSCT was better for persons not exposed to immunosuppressive DMT before the transplant, thus suggesting that aHSCT should be done early in the course of the disease and probably before the treatment with DMT. Additional studies are needed to further analyze the impact of the use of DMT therapies before the aHSCT in MS, as well as the timing of the procedure.

1. Introduction

Multiple sclerosis (MS) is the most common non-traumatic disabling disease to affect young adults. The incidence of the disease is increasing worldwide, together with the socioeconomic impact of the disease. The underlying cause of MS and mechanisms behind this increase remain

Abbreviations: aHSCT, Autologous Hematopoietic Stem Cell Transplantation; DMT, Disease Modifying Treatment; EDSS, Expanded Disability Status Scale; MS, Multiple Sclerosis; PBSC, Peripheral Blood Stem Cell; PROs, Patient-Reported Outcomes; RR, Response Rate.

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Table 1
Salient features of the 74 patients with multiple sclerosis followed for more than 36 months after autologous hematopoietic stem cell transplantation, exposed or not to prior disease modifying therapies. Response rate = sum of improvement or stabilization of the expanded disability status scale. RRMS = relapsing remitting multiple sclerosis. PPMS = primary progressive multiple sclerosis. SPMS = secondary progressive multiple sclerosis. [a] Mann–Whitney U test, [b] Chi squared test.

	Prior DMT	No-prior DMT	p
N	55	19	
Median age (range)	45 (40–54)	48 (42–54)	0.79[a]
Male	19	7	0.92 [b]
Female	36	12	
Years of evolution	9 (5–18)	6 (2–11)	0.79 [a]
RRMS	25 (45%)	4 (21%)	<0.05 [b]
PPMS	7 (12%)	10 (52%)	
SPMS	23 (42%)	5 (26%)	
Response rate at 12 mo.	72%	84%	>0.05 [b]
Response rate at 24 mo.	90%	84%	>0.05 [b]
Response rate at 36 mo.	67%	58%	>0.05 [b]

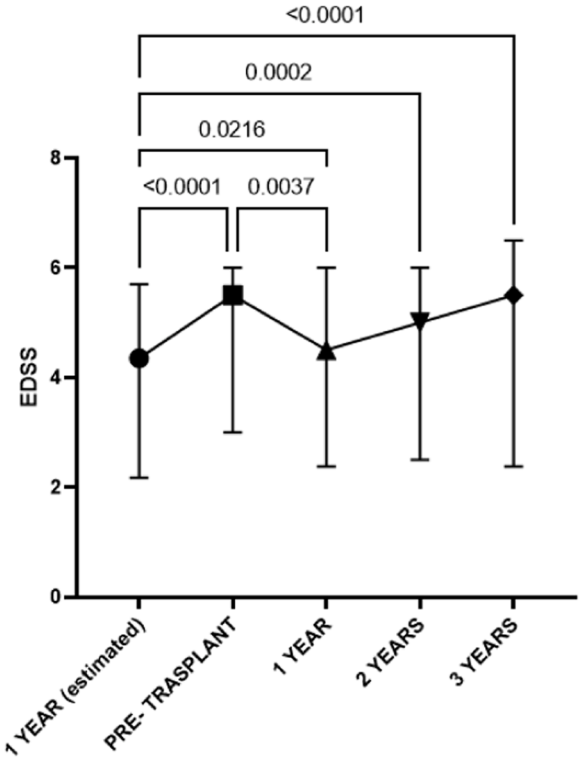

Fig. 1. Changes in the expanded disability status scale (EDSS) score in the whole group of 74 patients with multiple sclerosis followed for up to three consecutive years, given or not disease modifying treatments after the autologous hematopoietic stem cell transplantation. Data presented as median and IQR.

opaque, although complex gene-environment interactions may play a significant role. The epidemiology of MS indicates that infection with the Epstein-Barr virus, vitamin D deficiency, smoking, childhood obesity and others may have a role in disease development. Treatments for MS have increased exponentially in number, efficacy, and risk (Muraro et al., 2017) Autologous hematopoietic stem cell transplantation (aHSCT) has been identified as the most effective treatment for persons with MS (Patti et al., 2022), the rationale to conduct this procedure is the so called "re-booting" of the immune system aimed to ameliorate the immune-mediated inflammation and damage of the central nervous system structures (Dobson and Giovannoni, 2019). We have developed a method to conduct aHSCT in persons with MS and have shown its feasibility (Ruiz-Argüelles et al., 2017), safety (Gale et al., 2019) and usefulness (Ruiz-Argüelles et al., 2019) in a cohort of more than 1300 persons with the disease. We (Olivares-Gazca et al., 2022) and others (Mohammadi et al., 2021) have shown that the overall response rate of persons with MS given aHSCT is around 80%, as assessed by the change on the patient-reported outcomes (PROs) of the expanded disability status scale (EDSS) score (Signori et al., 2020), this figure being substantially better than that obtained employing several novel immunosuppressive drugs. When aHSCT was initally conducted in MS, 26 years ago (Bose and Freedman, 2021), it was thought that the procedure should be considered only after the failure of the response to other lines of treatments (Dargahi et al., 2017). Even though immunosuppressive therapy in MS is known as disease-modifying therapy (DMT), it seems clear that aHSCT is the only treatment which can change the natural history of the disease, since it is a more profound way of inducing immunosuppression. To analyze if aHSCT should be done early in the course of the disease or after failing to other therapies, we have studied the long-term results of aHSCT in a cohort of persons with MS who were given, or not, immunosuppressive drugs before the transplant.

2. Material and methods

2.1 Patients

All consecutive patients with MS referred to our center for a HSCT between June 2015 and January 2023 were prospectively entered in the study; 37 (50%) of the patients are originally from North America, 28 (28%) from Northern Europe, 6 (8%) from Western Europe, 2 (3%) from Oceania and 1 (1%) from Eastern Europe. Individuals with relapsing-remitting (RRMS), secondary progressive (SPMS) or primary progressive (PPMS) course were included. Patients should have a Karnofsky performance status above 70% and an expanded disability status scale (EDSS) score (Murrieta-Álvarez et al., 2021) of 8 or below in the two weeks prior to transplantation. None of the patients had received bone marrow damaging agents before being included in the study and all had a normal complete blood cell count when the mobilization was started. All patients had a wash-out period of at least three months of other immunosuppressive, DMT agents. The study was approved by the Ethics Committee of the Clinica RUIZ (*Conbioetica* 21CEI00120130605, Registry No. 13 CEI 21 114 126). All patients signed a consent form after being fully informed about the procedure and possible complications. Primary co-endpoints were recovery of granulocyte and platelet counts and TRM, whereas secondary endpoints were overall survival (OS) and response (improvement and stabilization of the EDSS score). Subjects were instructed to provide data of their neurologic evolution every three months posttransplant on special forms sent by e-mail. The protocol is registered in *ClinicalTrials.gov* identifier NCT02674217.

2.2 Peripheral blood stem cell mobilization and apheresis

The PBSC mobilization schedule was done with cyclophosphamide (Cy) and filgrastim (G-CSF). Intravenous Cy (50 mg/kg) was delivered in a 120-minute period on days –11 and –10. Subcutaneous G-CSF (10 μg / kg / bid) was delivered on days –9 to –1. Using either a peripheral vein or a Majurkar-type subclavian catheter, the apheresis procedure was performed on day –2, using an *Amicus* machine (*Fresenius Kabi*, Deerfield, IL, USA) or a *Spectra Optia* machine (*Terumo BCT*, Lakewood, CO, USA) and the Spin-Nebraska protocol ((Murrieta-Álvarez et al., 2021)). The apheresis objective was to reach at least 1×10^6 viable CD34+ cells/kg. CD34+ cells in peripheral blood were not measured before the apheresis procedures.

2.3 Conditioning and autografting

As outpatients and after collecting the targeted number of peripheral blood CD34+ cells, intravenous Cy (50 mg / kg) was delivered along a

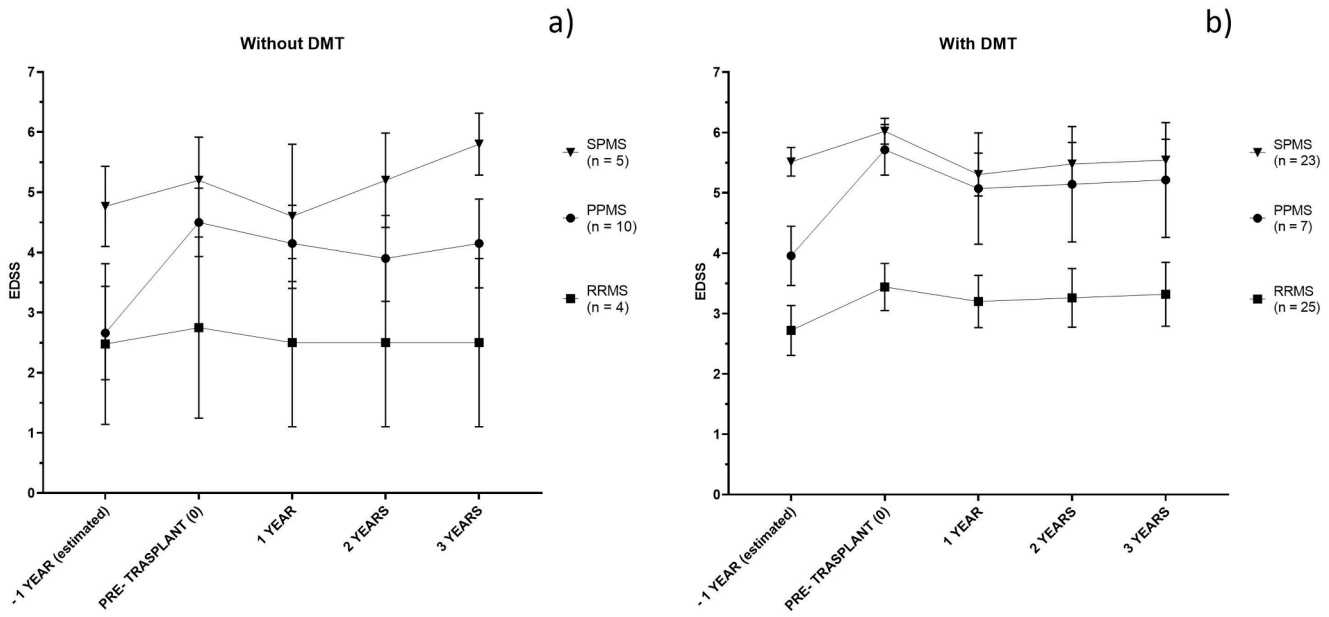

Fig. 2. Changes in the expanded disability status scale (EDSS) in the group of 74 patients according to the type of multiple sclerosis: Relapsing-remitting (RRMS), secondary progressive (SPMS) or primary progressive (PPMS). Panel a depicts patients who were not given disease modifying therapies (DMT), whereas panel b depicts patients given DMT. There is improvement or stabilization of the EDSS after aHSCT in the three types of MS. Data presented as mean ± SEM.

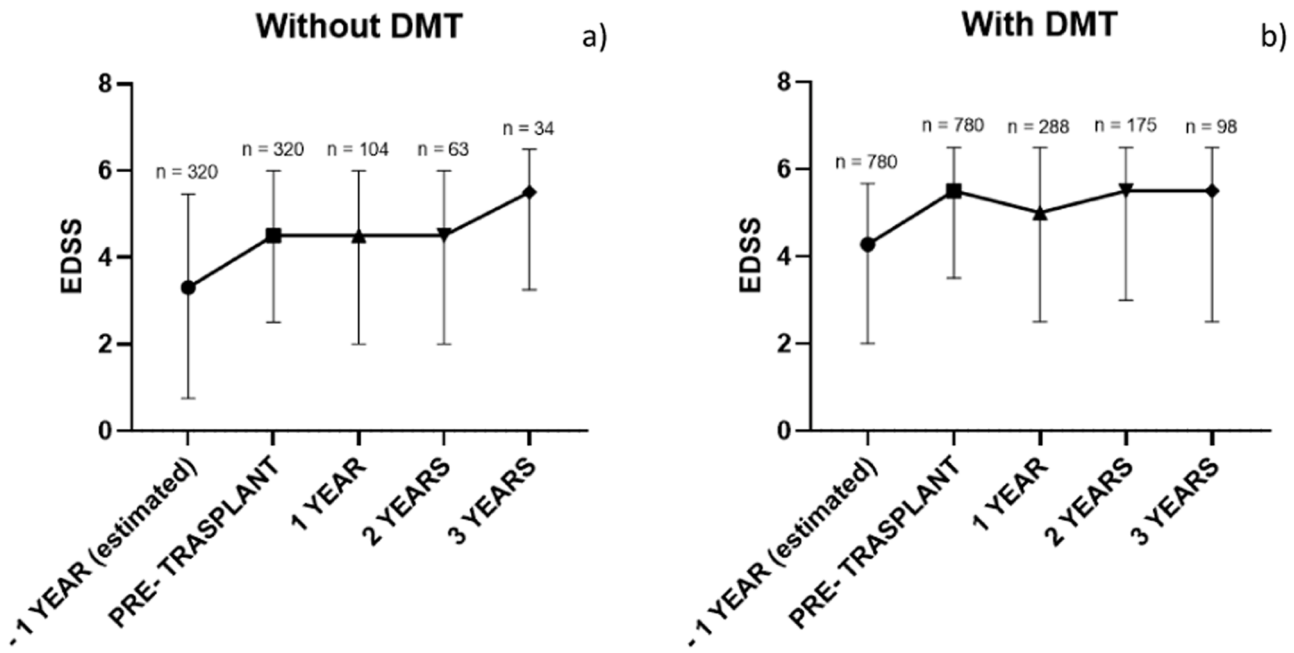

Fig. 3. Changes in the expanded disability status scale (EDSS) score in the patients with multiple sclerosis. Panel a depicts patients who were not given disease modifying therapies (DMT), whereas panel b depicts patients given DMT. Data presented as median and IQR.

120-minute period, on days –2 and –1 followed by MESNA (1000 mg/m2 along a 180-minute period), ondansetron 8 mg, dexamethasone 4 mg and pantoprazole 40 mg. After the intravenous Cy, ondansetron (4 mg every 12 h after chemotherapy), oral cotrimoxazole (800 / 160 mg every 24 h), oral fluconazole (200 mg) and oral acyclovir (400 mg every 12 h) were used in all patients until granulocytes were greater than 0.5×10^9/L; in this period all patients had laboratory workup and clinical studies every 48 h. As prophylaxis of both infections and MS relapses, in the following six months, cotrimoxazole 800/160 mg bid three times a week, and acyclovir 800 mg daily. The cumulative dose of Cy was 200 mg/kg. After the recovery of the granulocyte count, patients received a single high-dose of rituximab (1000 mg, fixed dose).

2.4 Apheresis product preservation, studies and infusion

The products of the apheresis and 1 ml aliquots were kept in ACD-A (*Baxter Healthcare*, Deerfield IL) at 4 °C, in 1000 ml transfer packs (*Baxter Healthcare*, Deerfield IL) composed of gas impermeable, polyvinyl chloride plastic film for up to 96 h. Enumeration of the total white mononuclear cells (MNC) and CD34 positive cells was done by flow-cytometry (Ruiz-Delgado et al., 2009) in an *EPICS Gallios* apparatus (*Coulter Electronics*, Hialeah FL, USA), using phycoerythrin labelled

Table 2
Disease-modifying or immunosuppressive therapies given to the 55 patients with multiple sclerosis who were subsequently given an autologous hematopoietic stem cell transplantation.

Disease modifying therapy	n
Interferon beta 1A and beta 1B	24 / 11
Glatiramer acetate	29
Dimethyl fumarate	23
Natalizumab	12
Fingolimod	7
Teriflunomide	4
Mitoxantrone	2

anti-CD34 HPCA-2 monoclonal antibody (*Becton Dickinson*, San José CA, USA) and a fluorescence isothiocyanate tagged anti CD45 monoclonal antibody (*Beckman Coulter, Hialeah, FLA, USA*), gating in 7′amino-actinomycin-D-excluding cells. Viability studies of the stored MNC used propidium iodide exclusion on the flow cytometer. The apheresis products obtained on day –1 were reinfused to the patients on day, after keeping them in a conventional blood bank refrigerator (*Thermoforma*, Marietta OH, USA).

2.5 Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the normality of the distribution of the data to be analyzed. Most of the parameters in our study do not conform to a normal distribution, so only Mann–Whitney U test was used to evaluate between-group differences. Chi squared statistic was used to test for categorical data. Data not normally distributed were presented as median and IQR and data normally distributed were presented as mean ± standard deviation. Results with p values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS 25 software (IBM Corp. Published 2017. IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.) and GraphPad Prism 9 (GraphPad Prism version 9 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com).

3. Results

3.1 Patients

1132 subjects were enrolled after June 2015. 408 were male (36%) and 724 female (64%). Median age was 46 y (range 39–53). 228 subjects (20%) had primary progressive MS, 555 (49%) relapsing remitting MS and 310 (27%) secondary progressive MS. Median EDSS score was 5 (range, 0 to 8) with an IQR of 3–6.5. All the autografts were started on an outpatient basis and only 35 persons needed to be admitted to the hospital during the procedure: 15 because of neutropenic fever, 2 as a result of MS flare-up, 3 to have a chest tube placed to solve a pneumothorax, 2 as a result of persistent nausea and / or vomiting and 13 each as a result of cardiac arrhythmia, rectal bleeding, urinary tract infection and minimal pleural effusion; all these patients required to stay in the hospital for a maximum of 48 h. In order to obtain a minimum of 1×10^6 viable CD34+ cells/kg 1 to 3 apheresis were needed (median 1). The total number of viable CD34+ cells infused to the patients ranged between 1 and 37.83×10^6 /kg (median 5.62×10^6/kg). A single apheresis procedure was enough to collect at least 1×10^6 /kg CD34+ cells in 83% of individuals. Patients recovered above 0.5×10^9/L absolute granulocytes on median day 8 (range 4 to 30) and above 20×10^9/L platelets on median day 6 (range 0 to 8). 96 individuals needed transfusions of red blood cells and 33 required platelet transfusions. The 36-month overall survival of the autografted patients is 99.8%. No opportunistic infections have been recorded.

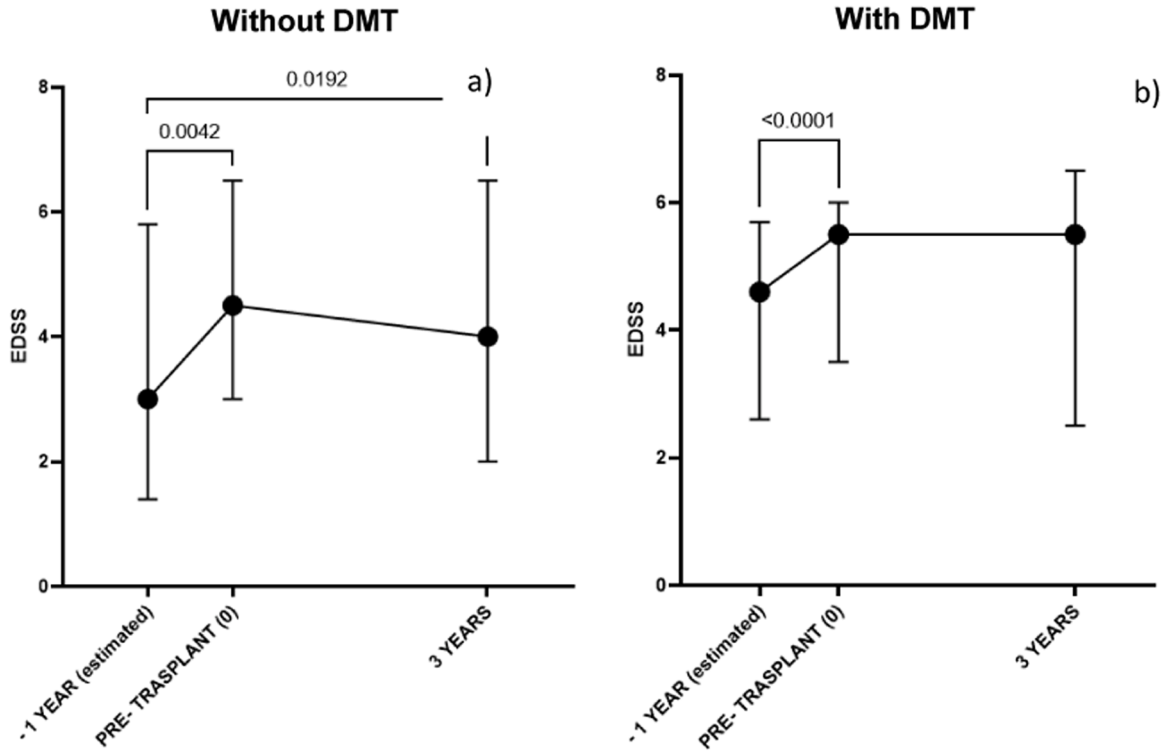

Fig. 4. a) Changes in the expanded disability status scale (EDSS) score in the group of 19 patients with multiple sclerosis not given disease-modifying therapies before the autologous hematopoietic stem cell transplantation. After an average estimated worsening of the EDSS score prior to the transplant it improved during the 3 years follow up dropping from 4.5 to 4. b) Changes in the expanded disability status scale (EDSS) score in the group of 55 patients with multiple sclerosis given disease-modifying therapies before the autologous hematopoietic stem cell transplantation. After an average estimated worsening of the EDSS score prior to the transplant it remained stable during the 3 years follow up at an average of 5.5. Data presented as median and IQR.

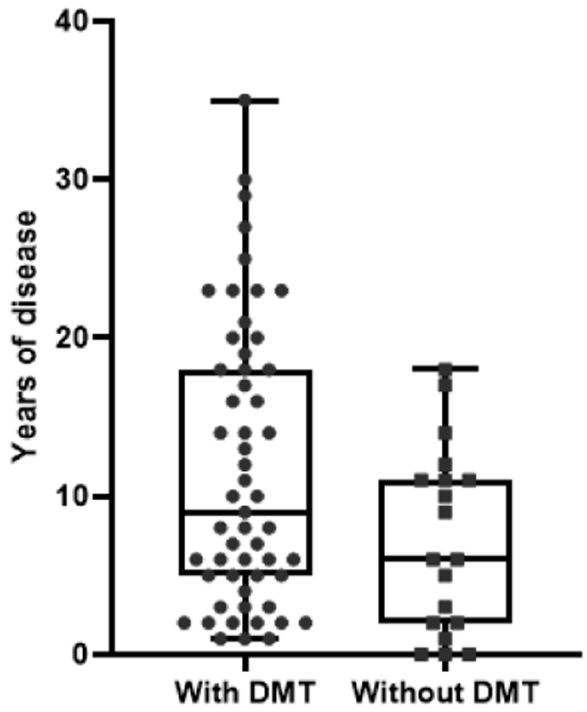

Fig. 5. Years of evolution of the multiple sclerosis before the autologous hematopoietic stem cell transplantation in patients who were or not given disease-modifying therapeutic (DMT) agents prior to the transplant. $p = .06$ Data presented as median and IQR.

3.2 Follow-up

Not all patients provided us with a response; accordingly, compliance was 32.6 percent at 6 mo, 34.6% at 1 year, 21% at 2 years and 6.5% at 3 years. 74 patients (6.5%) have been followed for more than 36 months and the subsequent analysis was done in this cohort. Of these, 32 (43%) reported improvement in the EDSS score and 16 (21%) reported stabilization, thus the response rate (RR = improvement + stabilization) was 48 / 74 = 65%. The RR at 12, 24 and 36 mo was 84%, 84% and 58% for patients not receiving prior DMT and 72%, 90% and 67% for patients receiving DMT, see Table 1. In the cohort of 74 patients, the EDSS dropped from a mean of 5.5 to a mean of 4.5 at 12 mo, to 5.0 at 24 mo and reached again 5.5 at 36 mo, after the aHSCT see Fig. 1. This suggests that the aHSCT-induced response is better at one year and subsequently drops during the following two years (see Fig. 1). The analysis of EDSS by MS type shows a decline after the first year from the aHSCT in the three types of MS, this drop is maintained at 2 and 3 years (Fig. 2), only in the patients with SPMS without DMT there is an increase of EDSS at 3 years, but there are only 5 patients in the group. No magnetic resonance imaging studies were systematically employed to assess the response.

3.3 Disease-modifying therapy

The Fig. 3 shows all the patients grouped according to the responses obtained and the history of treatment with DMT. It is observed that at 12 months post-transplantation responses were obtained in 392 patients, at 24 months in 238 patients and at 3 years in 132 patients. At 12 months there is no statistical difference in comparison with the pre transplant patient reported EDSS and at 24 months there is no statistical difference in comparison with the pre transplant patient reported EDSS and 12 months. In a subset of 74 patients we were able to record responses at 1, 2 and 3 years after the aHSCT; in this subset, 55 (74%) had received prior DMT, whereas 19 (26%) had not. The type of DMT given to the patients prior to the aHSCT is summarized in Table 2. In patients given DMT before the aHSCT, the transplant was able to stabilize the EDSS score at 3 years after the graft, whereas in persons not given DMT before the aHSCT, the transplant resulted in a significant decrease ($p = .01$) of the EDSS score (see Fig. 4). We estimated an average EDSS increase rate defined as EDSS score at the initial assessment prior to the transplant divided by the elapsed time since the disease onset. Compared to this estimated rate it is apparent that in patients given a DMT prior to the transplant on average were stabilized by the aHSCT, while those not given DMT significantly improved as a consequence of the transplant (Fig. 4). Accordingly, it seems that the conduction of the aHSCT improved the EDSS score in all patients, but even more in those not exposed to prior DMT, and that the use of DMT prior to the aHSCT somehow compromised the good response induced by the transplant. As expected, the time of the evolution of the disease was found to be longer in persons given DMT before the transplant than in those not exposed to this therapy prior to the graft, see Fig. 5.

4. Discussion

Long-evolution MS has an enormous impact in the quality of life for patients not just because of the physical disability and the mental and emotional component but also because of the high-cost treatments. The natural evolution of the disease in its relapsing form are episodes of neurological dysfunction alternated with partial or complete remission until the episodes develop into progressive neurological dysfunction and therefore physical disability; in the progressive phenotypes the neurological dysfunction begins and stays progressive over time (Hauser and Cree, 2020). The use of immunosuppressive DMT results in a reduction in the rate of relapses, in the accumulation of MRI lesions and in the improvement of disability in 20–50% of cases (Callegari et al., 2021), the best results apparently being those induced by ocrelizumab (McGinley et al., 2021). We have shown that the response rate (RR, improvement or stabilization of the EDSS score) to aHSCT employing our method is around 80% at 12 mo (Ruiz-Argüelles et al., 2017; Gale et al., 2019; Ruiz-Argüelles et al., 2019; Olivares-Gazca et al., 2022; Murrieta-Álvarez et al., 2021), and similar results have been obtained by others employing aHSCT in the treatment of MS (Sharrack et al., 2020). aHSCT has emerged as the best option of treatment for patients with MS because of its effectiveness and a lower cost in the long run. The concept of status of no evidence of disease activity (NEDA) is characterized by the absence of relapses, new MRI lesions and disability accrual (Giovannoni et al., 2017). The 2-year-pooled NEDA employing DMTs is around 48% (Muraro et al., 2017) and according to reports of the *European Blood and Marrow Transplantation Society* and the *American Society of Transplantation and Cellular Therapy*, the 2-year-pooled NEDA ranges from 70 to 92% employing aHSCT (Sormani et al., 2017), with a mortality of less than 0.2%. As a result, patients with MS are willing to travel to countries where aHSCT is performed and socioeconomic perceptions show that aHSCT is a one-time treatment that will reduce overall disease cost on the long term (Stathopoulos et al., 2021).

Despite not having consecutive follow-up in our entire sample, as shown in Fig. 3, the median EDSS in the 3 years after transplantation shows improvement or stabilization. In this study, conducted in persons with MS and a follow-up period of at least 36 months after the aHSCT, we have confirmed our previously informed reports about the response rate (RR, stabilization and/or improvement of the EDSS score) of around 80% (Ruiz-Argüelles et al., 2017; Gale et al., 2019; Ruiz-Argüelles et al., 2019; Olivares-Gazca et al., 2022; Murrieta-Álvarez et al., 2021). In addition, we have found that the RR was better for persons not exposed to immunosuppressive DMT before the transplant, thus suggesting that aHSCT should be done early in the course of the disease and probably before the treatment with DMT. We didnt find differences between males and females related to the response to the aHSCT.

This study has some limitations: a) the number of fully-followed patients in the cohort is limited, since, despite our efforts, we are losing follow-up data from many patients; b) As a result of the heterogeneity of the cohort, we are not able to analyze the effect of the

different types of DMT. Despite these caveats, our data seem to be useful recommend the timing of the aHSCT in the therapeutic chronology of persons with MSD.

Additional studies are needed to further analyze the impact of the use of DMT therapies prior to the aHSCT in MS, as well as the timing of the procedure.

CRediT authorship contribution statement

Daniela Sánchez-Bonilla: Conceptualization, Investigation, Writing – original draft. **Max Robles-Nasta:** Investigation, Data curation. **Moisés Manuel Gallardo-Pérez:** Conceptualization, Data curation, Methodology, Formal analysis, Writing – review & editing. **Edgar J. Hernández-Flores:** Investigation. **Merittzel Montes-Robles:** Investigation. **María de Lourdes Pastelín-Martínez:** Investigation. **Solón Javier Garcés-Eisele:** Writing – review & editing, Methodology. **Juan Carlos Olivares-Gazca:** Investigation. **Guillermo J. Ruiz-Delgado:** Supervision. **Guillermo J. Ruiz-Argüelles:** Supervision, Writing – review & editing, Methodology.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest.

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