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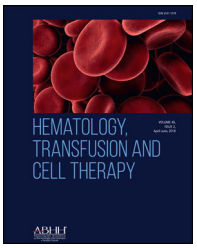

Review article

A review of hematopoietic stem cell transplantation for autoimmune diseases: multiple sclerosis, systemic sclerosis and Crohn's disease. Position paper of the Brazilian Society of Bone Marrow Transplantation

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ABSTRACT

Autoimmune diseases are an important field for the development of bone marrow transplantation, or hematopoietic stem cell transplantation. In Europe alone, almost 3000 procedures have been registered so far. The Brazilian Society for Bone Marrow Transplantation (Sociedade Brasileira de Transplantes de Medula Óssea) organized consensus meetings for the Autoimmune Diseases Group, to review the available literature on hematopoietic stem cell transplantation for autoimmune diseases, aiming to gather data that support the procedure for these patients. Three autoimmune diseases for which there are evidence-based indications for hematopoietic stem cell transplantation are multiple sclerosis, systemic sclerosis and Crohn's disease. The professional stem cell transplant societies in America, Europe and Brazil (Sociedade Brasileira de Transplantes de Medula Óssea) currently consider hematopoietic stem cell transplantation as a therapeutic modality for these three autoimmune diseases. This article reviews the evidence available.

Introduction

Autoimmune diseases have become an important field for the development of hematopoietic stem cell transplantation (HSCT). The European Society for Blood and Marrow Transplantation (EBMT) recently published an update of transplant indications for autoimmune diseases, with a total of 2809 cases registered at that point. The cases are summarized in Table 1.[1]

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Table 1 – Hematopoietic stem cell transplants for autoimmune diseases according to the European Society for Blood and Marrow Transplantation (EBMT).[1]

Autoimmune diseases		*n*
Multiple sclerosis	Total:	1415
Connective tissue diseases	Total:	771
Systemic sclerosis	609	
Systemic lupus erythematosus	110	
Polymyositis-dermatomyositis	17	
Sjogren's syndrome	4	
Antiphospholipid syndrome	6	
Other connective tissue diseases	25	
Rheumatoid arthritis (inflammatory arthritis)	Total:	190
Inflammatory bowel diseases	Total:	200
Crohn's disease	179	
Celiac disease	16	
Ulcerative colitis	2	
Other inflammatory bowel diseases	3	
Hematologic diseases	Total:	56
Immune thrombocytopenia	28	
Autoimmune hemolytic anemia	13	
Evans' syndrome	10	
Other hematological diseases	5	
Vasculitis	Total:	48
Granulomatous and polyangiitis	10	
Behcet's disease	9	
Takayasu's arteritis	3	
Polyarteritis	3	
Churg Strauss syndrome	2	
Other vasculitis	21	
Other neurological diseases	Total:	109
Insulin dependent diabetes	Total:	20
Other autoimmune diseases	Total:	23
Total		2809

Although autologous HSCT (AHSCT) has been used worldwide to treat autoimmune diseases, with slightly different approaches among centers, the main strategy remains similar. Briefly, the procedure consists of a first phase, when autologous hematopoietic stem cells are harvested and cryopreserved, and a second phase, including conditioning regimen and stem cell infusion. Patients undergo mobilization of hematopoietic stem cells from the bone marrow to peripheral blood through a combination of drugs including filgrastim (a granulocyte colony stimulating factor, G-CSF), followed by cell harvesting by leukapheresis and cryopreservation. Most transplant centers use 2–4 g/m^2 cyclophosphamide and granulocyte colony-stimulating factor (G-CSF) for subsequent collection of hematopoietic progenitor cells.[2–13] The scheme allows for collection of more cells than the use of G-CSF as a single agent, and very few events of mobilization failure are described. Additionally, the administered cyclophosphamide promotes initial control of disease activity, contributing to the therapeutic effect of the transplant procedure.[10,11,13]

At the second phase of HSCT, patients receive immunoablative doses of a lymphoablative conditioning regimen that may include chemotherapeutic agents, immunotherapeutic agents and/or irradiation, followed by autologous cell infusion. A period of aplasia follows, after which there is engraftment and reconstitution of a tolerant and no longer self-reactive immune system.[10,14] The purpose of HSCT in autoimmune diseases is to promote immune depletion, eliminate autoreactive lymphocytes, and to reprogramme the immune system, leading to the reestablishment of immune tolerance and, thereby, prolonged disease control.[15]

The Brazilian Society for Bone Marrow Transplantation (Sociedade Brasileira de Transplantes de Medula Óssea, SBMTO) organized consensus meetings for the Autoimmune Diseases Group, to review the available literature on HSCT for autoimmune diseases, aiming to gather evidence that support the procedure for these patients. Three of the most important indications for HSCT, sufficiently evidence-based, are multiple sclerosis (MS), systemic sclerosis (SSc) and Crohn's disease. As the following sections show, the American Society for Transplantation and Cellular Therapy (ASTCT), the European Society (EBMT), and the Brazilian SBMTO currently consider HSCT as part of the already consolidated treatment procedures for these three autoimmune diseases, outside research trial settings.

Multiple sclerosis

Multiple sclerosis (MS) is a demyelinating chronic inflammatory disease of the central nervous system that mainly affects young adults, and has heterogeneous clinical and pathological characteristics resulting from different pathways of tissue injury.[16] Inflammation, demyelination, and axonal degeneration are the main pathological mechanisms that cause clinical manifestations.[17] However, the cause of MS is unknown[18,19] and it is considered an incurable disease. The most widely accepted theory is that MS begins as an autoimmune inflammatory reaction mediated by autoreactive lymphocytes.[16,20] Microglia activation and chronic neurodegeneration occur later. Regardless of the immune pattern of early demyelination, analyzes of active lesions over time suggest that there is a single immuno-effector mechanism in each person.[21]

MS begins at the median age of 23.5 years, and mean age of 30 years.[22] Mortality among patients with MS is not much different from the general population, but neurological deficits progress in all patients. It is expected that in 15 years from diagnosis, 50% of patients will need help walking, and after 25 years, most cannot walk anymore.[23,24]

MS symptoms are non-specific and may include paresthesias and paresis due to transverse myelitis, ataxia due to cerebellar injury, tremor, monocular visual loss due to optic neuritis, double vision due to brainstem dysfunction, fatigue and sphincter changes. If there is a relapse episode, the functional disability scale score used in neurological examination increases, indicating worsening. During remission, the patient remains stable within his or her disability score. Numerous scales have been described to evaluate MS, the most used being the Expanded Disability Status Scale (EDSS), described by Kurtzke.[25]

MS is classified in three clinical types, which receive different treatment approaches. The first is the relapsing remitting type (RRMS), resulting from inflammatory multifocal lesions that cause clinical recurrence and activity of detectable lesions on magnetic resonance imaging (increase or appearance of new lesions on hyperintense T2 or increase of gadolinium on

T1 lesions). It manifests with episodic relapses followed by partial or total recovery from dysfunction, interspersed with remission periods of at least 30 days.[23,24]

After an average time of 10–15 years, the episodes become less frequent, followed by less evident recovery, with accumulation of sequelae and gradual worsening of the neurological picture that is typical of the secondary progressive form (SPMS). This is characterized by neurodegeneration, but may still have superimposed inflammatory activity.[23,24]

The third clinical type of MS, the primary progressive MS (PPMS), occur in about 10–15% of patients, at the mean age onset of approximately 40 years, and occurs equally in males and females. It is characterized by progressive accumulation of disability from disease onset. Can occur occasional plateaus, minor and temporary improvements but after all continues progressing. The diagnosis is made based only on patient's history. This "malignant form" or "aggressive form" of MS, is characterized by rapidly progressive course, leading to significant disability, or even death, in multiple neurologic systems in a relatively short time after disease onset.[23,24]

The worsening of symptoms is highly heterogeneous among patients with MS. The extent of inflammatory activity affects MS prognosis substantially. Because of that, the goal of treatment approaches is the absence of disease activity clinically or at magnetic resonance imaging and the improvement of disability or of the EDSS score. This is called "no evidence of disease activity" (NEDA).[26]

Conventional therapeutic approaches for multiple sclerosis

As of December 2017, the US Food and Drug Administration (FDA) has approved 15 drugs considered as capable of modifying MS course: 5 interferon-beta preparations; two glatiramer acetate preparations; the monoclonal antibodies natalizumab, alemtuzumab, daclizumab and ocrelizumab (the first B-cell targeted therapy); the chemotherapeutic agent mitoxantrone; and small molecule oral agents fingolimod, dimethyl fumarate and teriflunomide. Dalfampridine (aminoperidine) has been approved as a therapy to treat and improve gait speed.[21] However, none of these are curative therapies. They are partially effective in reducing relapse rates and disease progression. Furthermore, all disease-modifying therapies present safety concerns, with the risk increasing over time. Better treatment strategies are required for patients with relapsing MS, for those who present inflammatory activity despite the treatment used and for those with treatment side effects.[27]

Transplant in multiple sclerosis

Since the mid-1990s, with the first studies on animal models with subsequent clinical application, autologous transplantation (AHSCT) has been an important tool in inducing an "immunotolerant" immune reconstitution.[2,3] Thousands of transplants for treating MS have been performed worldwide, with more than 700 evaluated in studies.[6,28–46] Some studies showed progression-free survival of more than five years,[39,43] with superior neurological improvement in patients with relapsing-remission type and in those with inflammatory activity observed on magnetic resonance imaging.[43,47,48] Table 2 shows the results of the main studies focused on the use of HSCT to treat MS: there are 8 retrospective studies and 6 single-arm clinical trials on AHSCT for MS, and only 2 randomized clinical trials focusing on the comparison of AHSCT versus disease-modifying therapies for MS. There are also 3 meta-analysis and systematic reviews and one position paper.[6,9,10,39,49–57]

These studies together support the efficacy of AHSCT in patients with relapsing form of MS. Although they differed in design, population, conditioning protocol and only two were randomized with a control group, many patients experience disease activity control for a long time. The largest retrospective study was a review from the CIBMTR/EBMT register in 2017 that analyzed 281 patients.[53] Overall progression-free survival rate was 46%; among patients with RRMS or PRMS, progression-free survival rates were 82% at 3 years and 73% at 5 years; OS at 5 years was 93%. Factors associated with neurologic progression post AHCT was older age, progressive versus relapsing form of MS and more than two previous disease modifying therapies (DMTs).

All the single-arm[35,58–63] clinical trials demonstrated high efficacy of AHSCT for RRMS or PRMS. The first reported was by Burt et al., with 21 patients with RRMS conditioned with cyclophosphamide plus rabbit ATG/alemtuzumab, showing a EDSS progression free survival at 3 years of 100% and EDSS improvements $\geq$1 in 81% and no change in 9.5%, OS of 100%.[59] Recently Moore at al. reported 35 patients with RRMS and SPMS in a phase 2 study conditioned with BEAM and horse ATG showing a MS activity-free survival of 82% at one year 65% at 2 years and 60% at 3 years; looking at RRMS only the MS activity-free survival was 90% at one year and 70% at 3 years.[63]

Only two randomized controlled trials are available: in the ASTIMS study, Mancardy et al. compared AHSCT versus mitoxantrone; 9 out 21 were randomized to AHSCT.[52] They were conditioned with BEAM plus rabbit ATG. Over 4 years, the median number of new T2-weighted MRI lesions was 2.5 in the AHSCT versus 8 in the mitoxantrone group ($p = 0.00016$) and none of those who received AHSCT had new gadolinium-enhanced MRI lesions, but 56% of those on mitoxantrone had at least 1 MRI lesion ($p = 0.029$); EDSS progression was 57% in AHSCT vs 48% in the mitoxantrone group ($p = 0.50$). The phase 3 MIST trial[55] compared the efficacy of AHSCT versus DMTs. The conditioning was non-myeloablative, with cyclophosphamide plus rabbit ATG and 110 patients were randomized 1:1. With a follow-up of up to 5 years, disability worsening occurred in 5.8% AHSCT versus 66.7% of DMT group. At 1 year, relapse occurred in 2% in the AHSCT and 68.2% in the DMT group 9; with $p < 0.001$ and at 5 years, relapse occurred in 15.4% AHSCT vs 85.2% DMT group; no deaths or grade 4 toxicities related to transplantation were reported.

A meta-analysis of AHSCT for MS evaluated the safety and efficacy of transplant. Led by Somani at al., it evaluated 15 studies including more than 764 transplanted patients. A proportion of NEDA (no evidence of disease activity) was found in 2 years in 83% and in 5 years 67%; the transplant-related mortality was estimated in 2.3%, the rate of EDDS progression was 17.1% at 2 years and 23.3% at 5 years.[54] Another interesting study done by Sormani et al.[64] evaluated a comparison of NEDA status in studies of AHSCT ($n = 66$) with various conventional e high-efficacy MS DMTs ($n = 216$). The use of AHSCT led

Table 2 – Results of studies on multiple sclerosis disease.

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria/	N	Transplant regimen	PFS/outcomes	Relapse/ progression rate	Non-relapse mortality	OS	Follow-up
Retrospective studies											
Italy 2012[49]	Retrospective case series	None	EDSS progression free-survival	MS treated previously with DMT with severe clinical course past year (EDSS worsening ≥ 1.0)	74 (33 RRMS and 41 SPMS)	BEAM + rabbit ATG	EDSS PFS at 5y 66% for all patients RRMS EDSS PFS 5y 71%	30% for RRMS vs 10% for SPMS	2.7%	95.9%	Median 4 years (8 mo–10.5 yrs)
Swedish 2014[56]	Retrospective case series	None	Relapse free survival, MRI event free survival, EDSS PFS and DFS	MS treated previously with DMT	52 but analyzed 41 (40 RRMS, 5 SPMS, 2 PPMS,)	BEAM + ATG in 41 and Cy (200 mg/kg) + ATG in 7	At 5y: EDSS PFS 77%; clinical relapse free survival 87%; MRI event-free survival 85% and DFS: 68%	At 5 years, 4 patients had clinical relapse, 5 had MRI activity, 8 had EDSS progression	Zero TRM	100%	Mean 4.0 years (1–9 yrs)
Northwestern/Chicago 2015[55]	Retrospective case series	None	Time to EDSS improvement and time to EDSS worsening both at least 1.0 point	RRMS failed DMT, with 2 or more treated relapses or 1 treated relapse with Gd lesion at a separate time/RRMS 123, SPMS 28	151 but 145 analyzed	CY 200 mg/kg + alentuzumab 20 mg or rabbit ATG 6 mg/kg	EDSS improved 50% at 2 years, 64% at 4 years Relapse-free survival was 89% at 2 years and 80% at 4 years; PFS was 92% at 2 years and 87% at 4 years and disease activity–free survival was 80% and 68% respectively	The proportion of patients with a 1.0 or greater change in EDSS score was 10% in 19 of 112 patients with an indication of progression at 1 year and 11% in 9 of 82 for progression at 2 years; and 11% in 7 of 64 for progression at 3 years; and 8% in 3 of 36 for progression at 4 years; and 5% in 4 of 27 for progression at 5 years.	Zero TRM	99.3% (1 death due hypertensive cardiovascular disease)	2,5 years (6 month–5 yrs)

Table 2 – (*Continued*)

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria/	N	Transplant regimen	PFS/outcomes	Relapse/ progression rate	Non-relapse mortality	OS	Follow-up
CIBMTR/EBMT Review[53]	Retrospective registry review	None	PFS	Data base of AHSCT for MS/46 RRMS, 186 SPMS, 32 PPMS, 17 PRMS	RRMS failed DMT, with 2 or more treated relapses or 1 treated relapse with Gd lesion at a separate time/RRMS 123, SPMS 28	High intensity in 53/281 (18.9%); intermediate intensity in 49/281 (17.4%); low intensity in 49/281 (17.4%).	Overall PFS was 46%; among patients with RRMs/PRMS PFS was 82% at 3 years and EDSS PFS 73% at 5 years		2.8%	93% at 5 years	Median 6.6 yrs
Czech Republic 2010[39]	Retrospective case series	None	Reported efficacy of AHSCT experience in MS	All patients treated with AHSCT 10 years 11 RRMS, 15 SPMS	Data base of AHSCT for MS/46 RRMS, 186 SPMS, 32 PPMS, 17 PRMS	BEAM in 26 and BEAM + ATG in 16	PFS at 3 years 70.8% and 29.2% at 6 years	Median annual relapse rate within the year before ASCT was 2, while the median annual relapse rate was 0 within the first 2 years after ASCT	Zero	96.1% (1 death due to glioblastoma multiforme at 60 months of follow-up)	Median 66 months (11–132)
Spain 2017[57]	Retrospective case series	None	Reported toxicity and the long-term efficacy of AHSCT	RRMS/SPMS under treatment with one of the MS-approved drugs for more than 1 year, who experienced one or more relapses in the previous year and worsening of at least 1 point in disability (EDSS) 22 RRMS, 9 SPMS	31	BEAM + rabbit ATG	100% of RRMs were free of disability at 6 months; and 60% achieving sustained disability recovery at 6 months; 22% of SPMS were free of disability at 6 months; and 10% achieving sustained disability recovery at 6 months	32.3% (10) had at least one relapse post-AHSCT; 6 in the RRMS group (27.2%) and 4 in the SPMS group (44.4%). 7 (22.6%) experienced progression of disability, all within SP form.	Zero	96.7% (1 death 13 years after transplant from aspiration pneumonia after progressing and reaching an EDSS of 9.5.)	Median 8.4 years (2–16)

Table 2 – (*Continued*)

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria/	N	Transplant regimen	PFS/outcomes	Relapse/ progression rate	Non-relapse mortality	OS	Follow-up
Single-arm prospective study											
Russia 2015[58]	Single arm clinical trial	None	Safety and efficacy (treatment response)	All patients treated with AHSCT 6 years: EDSS 1.5–8.0, ±Gd lesions, and no treatment with interferons or immunosup-pressive agents within 3 months before enrollment	99 (43 RRMS, 56 SPMS, 18 PPMS, 3 PRMS)	Reduced intensity conditioning regimen based on BEAM	EFS for the whole group was 80%. In the group with RRMS, EFS was 83.3% and in the group with progressive course 75.5% 92% EDSS PFS 5 years	16.7% at 8 years.	Zero	100%	Median 48.9 months
Northwest-ern/Chicago 2009[59]	Single arm clinical trial	None	EDSS PFS and reversal of neurologic disability	RRMS with 2 steroid treated relapses in previous 12 month.	21 (21 RRMS)	Cychophos-phamide + alemtuzumab /rabbit ATG	100% EDSS PFS 3 years	5 patients (24%) relapsed but achieved remission after further immuno-suppression After a mean of 37 months (range 24–48 months), all patients were free from progression (no deterioration in EDSS score), and 16 were free of relapses	Zero	100%	Mean 3.1 years (1.5–10)
Canada 2016[62]	Single arm clinical trial	None	MS activity-free survival (absence of clinical relapse, new MRI lesion or progression of EDSS)	Disease activity despite 1 year of DMT.	24 (12 RRMS, 12 SPMS)	Cyclophos-phamide/ busulfan	70% PFS 3 years	No clinical relapse	4.2%	95%	Median 6.1 year (±2.5)

Table 2 – (*Continued*)

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria/	N	Transplant regimen	PFS/outcomes	Relapse/ progression rate	Non-relapse mortality	OS	Follow-up
HALT-MS 2015, 2017[60,61]	Single arm clinical trial	None	Time to treatment failure (death or MS activity)	RRMS with failure of DMTs during the prior 18 months	24 (24 RRMS)	BEAM + rabbit ATG	70% NEDA 5 years, 91% EDSS PFS	Two participants had disease progression and died at .2.5 years and .3.5 years after AHSCT; a third participant also had disease progression at 15 months and died at 4.5 years post-HCT Of 24 patients 7 did not maintain EFS by close of follow-up by an increase in EDSS 0.5 ($n = 2$), clinical relapse ($n = 3$) or development of new MRI lesions ($n = 2$)	Zero	87.5%	Median 4.9 year (6–12)
Australia 2018[63]	Single arm clinical trial	None	EFS (NEDA)	RRMS with at least 1 relapse or one new MRI lesion in the past year despite DMT/SPMS worsening with at least 1 MRI lesion in the past year.	35 (20 RRMS, 15 SPMS)	BEAM + horse ATG	60% NEDA 3 year	Clinical relapses occurred in 3 patients at 12, 13 and 14 months, respectively after AHSCT	Zero	100%	Median 6.9 year (0.7–21.6)
Randomized study											
ASTIMS 2015[52]	Phase II, AHSCT vs mitoxantrone	AHSCT vs mitox-antrone	Cumulative number of new T2 lesion MRI 4 years after random-ization	Worsening in EDSS and one or more MRI lesion last year despite DMTs	21 (9 to AHSCT) 7 RRMS, 13 SPMS, 1 PPMS	BEAM + ATG	New T2 lesion MRI: 2.5 AHSCT vs 8 mitoxantrone 4 years	EDSS progression was 57% in AHSCT vs 48% in the mitoxantrone ($p = 0.5$)	Zero	100%	4 years

Table 2 – (*Continued*)

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria/	N	Transplant regimen	PFS/outcomes	Relapse/ progression rate	Non-relapse mortality	OS	Follow-up
MIST 2018[55]	Phase3 AHSCT vs conventional DMT	AHSCT vs DMT	6-Month worsening EDSS $\geq$ 1.0 after one year's post-AHSCT or DMT treatment	At least 2 clinical relapse, or one relapse in MRI lesion at different time in the last year despite DMT	110 (55 AHSCT) 110 RRMS	Cyclophos-phamide + rabbit ATG	At 1 year, mean EDSS improved from 3.38% to 2.36% with AHSCT and worsened from 3.31 to 3.98 with DMTs. At 1 year, mean T2 lesion volume on MRI decreased in the AHSCT, but increased in The DMT group.	15.4% AHSCT vs 85.3% of relapse at 5 years. Disability worsening occur in 5.8% AHSCT vs 66.7% DMT group; median time to pression 24 months in the DMT.	Zero	100%	Up to 5 years

N: number of enrolled subjects; PFS: progression-free survival; OS: overall survival; EDSS: Expanded Disability Status Scale; TRM: transplant-related mortality; FU: follow-up; AHSCT: autologous hematopoietic stem cell transplantation; SPMS: secondary progressive MS; PPMS: primary progressive MS; PRMS: progressive relapsing; DMT: disease modifying treatment; NEDA: no evidence of disease activity (absence of relapse, disability worsening on the EDSS or MRI lesion activity); MRI: magnetic resonance imaging; Gd: gadolinium-enhanced lesion on MRI.

Box 1: Indications for autologous[a] hematopoietic stem cell transplantation (HSCT) in multiple sclerosis (MS).

Patients under 60 years old who are not responsive to the current first line standard therapy and who present EDDS between 3 and 6

Patients with inflammatory activity in the forms:
- relapsing-remitting: IB;
- secondary progressive with inflammatory activity (clinical and imaging): IIB;
- primary progressive with inflammatory activity (clinical and imaging): IIB

Patients with the "malignant" form of multiple sclerosis who developed severe disability in the previous year: IIB

EDSS: Expanded Disability Status Scale.
[a] Allogeneic HSCT is not recommended for any category of MS.

Box 2: Contraindications to hematopoietic stem cell transplantation in multiple sclerosis.

- Advanced disease and no inflammatory activity
- EDSS > 6.0
- Renal impairment: serum creatinine > 2 mg/dL (177 μmol/L) or creatinine clearance (CrCL) < 50.
- Liver dysfunction: Frank cirrhosis. Other condition related to liver dysfunction (hepatitis, alcohol abuse, hepatic steatosis and iron overload) need consultation with a hepatologist to contraindication
- Cardiac disease: left ventricular ejection fraction (LVEF) ≤40% for BEAM condition and LVEF ≤50% using chemotherapy regimens with known cardiac toxicity (e.g., cyclophosphamide) or uncontrolled coronary artery disease or uncontrolled arrhythmias.
- Pulmonary dysfunction: corrected DLCO < 50%
- Poorly controlled chronic diseases (diabetes, hypertension)
- Pregnancy
- HIV positivity
- History of previous malignancy
- Psychiatric disorders

EDSS: Expanded Disability Status Scale.

to NEDA rates of 78–83% at 2 years and 60–68% at 5 years. On the other hand, DMTs lead to reported NEDA rates of 13–46% at 2 years.

Transplant-related mortality (TRM) has improved over the past 20 years.[14,54] The initial reports described TRM as high as 9.5% (37, revised in 65), which later decreased to 1.3%, according to EBMT data.[6,9] The incorporation of less myeloablative regimens, center experience and center accreditation have contributed to the improved outcomes.[8,59,65–68]

Recently the American Society of Bone Marrow Transplantation[50] has conducted a comprehensive literature review, including many of the papers already discussed here, and recommended autologous HSCT as "standard of care, clinical evidence available" for treatment-refractory relapsing MS.

Guidelines for transplantation in multiple sclerosis

Considering the results presented above, HSCT can be considered for patients with relapsing-remitting form of MS, with EDSS less than 6, who have not responded to conventional treatment or progressive MS with superimposed activity. Especially if disease activity continues despite treatment with high-efficacy DMTs and worsening disability. The treatment for other MS types should follow the guidelines proposed by SBMTO previously,[69] shown in Box 1 and Box 2, and using the same reduced-intensity conditioning with cyclophosphamide (200 mg/kg) and rabbit anti-thymocyte (4.5 mg/kg). Intensive vigilance should be maintained for short and long-term post-transplant complications, especially fever, deep vein thrombosis, pulmonary embolism, urinary tract infections, falls, metabolic syndrome and coronary disease.[65,70]

Systemic sclerosis

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by fibrosis of the skin and internal organs, and vasculopathy.[71,72] The disease usually begins with vascular hyperreactivity and endothelial activation, which, associated with inflammatory phenomena, promotes progressive tissue damage and fibrosis.[73] The etiology, still not completely understood, includes a susceptible genetic background associated with environmental stimuli, which promote immune dysregulation and, as a consequence, injury to tissues.[71,73]

Patients with severe and progressive forms of SSc have reduced quality of life and mortality rates that can reach 50% in five years and 70% in 10 years.[74] Cardiopulmonary dysfunction is the leading cause of death, especially in patients with interstitial lung disease and pulmonary hypertension.[71] A meta-analysis has shown that the mortality of patients with SSc has not decreased in the past 40 years, despite new available treatment options.[75]

Clinical presentation

Skin involvement is a hallmark of SSc, and its extent enables clinical classification into three subtypes: limited, diffuse and *sine scleroderma* (without cutaneous involvement). The extent of skin involvement correlates with disease presentation and severity. Patients with the diffuse form of SSc suffer from interstitial lung disease, cardiac and renal involvement more frequently.[72] This subtype tends to progress faster and with greater severity, morbidity and mortality than other forms of the disease.[72,76,77] On the other hand, limited systemic sclerosis patients tend to present pulmonary hypertension as a life-threatening manifestation.

Conventional therapeutic approaches

The management of patients with systemic sclerosis (SSc) includes pharmacological and non-pharmacological approaches.[78] Hand and extremity warming and protection against trauma, dietary and postural measures to reduce gastroesophageal reflux and treatment of skin and digital ulcers are recommended for most patients, given the high frequency of these manifestations.[78]

Conventional drug treatment is quite limited and ineffective in controlling the progression of the disease. There are no drugs that treat SSc globally, and therapeutic strategies are often organ or manifestation-directed. Currently, international rheumatology societies have developed recommendations for the treatment of patients with SSc, always according to individual manifestations.[78,79] Randomized clinical studies have investigated synthetic and biological immunomodulatory agents, showing modest benefits and no repercussions on disease-related mortality, with exception of angiotensin-converting enzyme (ACE) inhibitors, which in the past significantly decreased the mortality of patients with scleroderma renal crises.[59,78]

Interstitial lung disease is a severe manifestation of SSc and the leading cause of death in this disease. The available treatments have modest and short-lived success rates on the control of interstitial lung disease.[71,78–81] Best outcomes are described for cyclophosphamide and mycophenolate mofetil, with short-term benefit when compared with placebo.[82,83] More recently, rituximab, tocilizumab, nintedanib and pirfenidone, among other therapeutic agents, have been investigated with promising results, yet to be confirmed.[84–87] Isolated diffuse skin involvement, when severe and progressive, is also associated with high mortality rates and poor quality of life, with outcomes comparable to those of patients with visceral involvement.[86] Thus, systemic immunosuppression is recommended for selected cases.[87]

Hematopoietic stem cell transplantation

In the past years 20 years, AHSCT has been indicated as treatment for patients with severe and rapidly progressive SSc.[10] According to data from international transplant registries, the number of transplanted patients per year has progressively increased, reflecting the good outcomes of this therapeutic approach.[14]

The most recently adopted indication criteria for transplantation are the following[10,88,89]:

- An established diagnosis of systemic sclerosis, according to the 2013 ACR/EULAR classification criteria[90].
- Patients with diffuse form of the disease, with a minimum modified Rodnan's score of 16, and worsening by at least 25% in the last 6 months, under immunosuppressive treatment.
- Patients with interstitial lung involvement with a decline in predicted forced vital capacity (FVC) or carbon monoxide (CO) diffusion percentages greater than 10% in the preceding 6 months, while under immunosuppressive treatment.

The exclusion criteria for HSCT to consider based on available studies are the following[10,88,89]:

- Age over 60 years;
- Current pregnancy;
- Inability to practice effective contraception;
- Inability to accept infertility as a possible consequence after transplantation;
- Severe psychiatric disorder;
- Current acute or chronic infection;
- Previous malignancy, except localized and treated cervical and thyroid cancer;
- Major organ dysfunction, as follows:
  - Liver – increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST), over three times the normal range; or increased serum bilirubin levels, over three times the normal range, except when Gilbert's syndrome present;
  - Kidneys – creatinine clearance below 40 ml/min; or creatinine levels above 2 mg/dL;
  - Lungs – forced vital capacity or hemoglobin-adjusted CO diffusion below 40% of predicted;
  - Heart – left ventricular ejection fraction below 50%, constrictive pericarditis, ventricular arrhythmias, extensive myocardial fibrosis, systolic pulmonary artery pressure greater than 40 mmHg or mean pulmonary artery pressure greater than 25 mmHg, evidence of ventricular diastolic dysfunction, septal dyssynergia.

Historically, the initial studies were important to establish recommendations and guide currently adopted procedures. Phase I/II studies showed that autologous HSCT (AHSCT) improves skin involvement and at least stabilizes the pulmonary condition (Table 3).[11,12,91–96] These studies also evidenced the importance of a proper heart assessment as a strategy to decrease transplant-related mortality. Cardiac dysfunctions that occur during transplantation accounted for many of the transplant-related deaths described in the initial studies.[97] Currently, there are detailed cardiac assessment recommendations,[98] aimed at identifying patients with previous cardiac lesions and, therefore, at a higher risk of cardiotoxicity.

The three randomized studies more recently published show that HSCT surpasses conventional treatment in SSc patients, promoting longer overall survival, longer disease-free survival and higher quality of life (Table 3).[88,99,100] These results are essential to convince the community about the efficacy of HSCT. In fact, since 2017, AHSCT has been recommended by the European League Against Rheumatism (EULAR) guidelines, for patients with SSc at risk of organ failure.[78]

Treatment protocols have been refined and incorporated into the routine of several transplant centers. However, a few points of debate still remain. There is still no consensus among centers whether to adopt graft selection or to use non-selected grafts. While CD34+ graft selection may prevent reinfusion of autoreactive cells during transplant and potential disease reactivation, it adds costs to the procedure and increases the risk of contamination and cell death. A retrospective study from the European Blood and Marrow Transplant Group

Table 3 – Results of studies on systemic sclerosis disease.

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria	N	Transplant regimen	PFS	Relapse/ progression rate	Non-relapse mortality	OS
Single-arm studies										
Europe + USA multicenter/2001[91]	Phase I/II	None, single arm	Feasibility, mortality and preliminary response to treatment	Diffuse SSc or limited SSC with interstitial lung disease *or* pulmonary hypertension	41 (37 transplanted)	Multiple, most CY 150–200 mg/kg ± ATG/alemtuzumab and/or TBI	46% at 4y	23% (7/30) at 4y	17% (7/41)	73% at 4y
France multicenter/2002[93]	Phase I/II	None, single arm	Feasibility, tolerance and efficacy	Early (<4y) diffuse SSc plus visceral involvement	12 (11 transplanted)	CY or Melphalan CD34+ selected graft	45% at mean 18 months	50% (5/10) at mean 18 months FU	9% (1/11)	64% at mean 18 months FU
USA multicenter/2002[104]	Pilot study	None, single arm	Safety and potential efficacy	Early (<3y) diffuse SSc plus visceral involvement *or* progressive interstitial lung disease	19	TBI 800 cGy + CY 120 mg/kg + 90 mg/kg eATG CD34+ selected graft	63% at mean 15 months	25% (4/16) at mean 15 months	16% (3/19)	79% at mean 15 months
Europe multicenter/2004[94]	Retrospective analysis of phase I and II studies	All studies were non-comparative, single arm	Safety and efficacy	Early (<3y) diffuse SSc *or* progressive interstitial lung disease	57	Multiple, most CY 150–200 mg/kg ± ATG/alemtuzumab and/or TBI	58% at 5y	48% at 5y	8.7% (5/57)	72% at 5y
USA multicenter/2007[95]	Phase II	None, single arm	Safety and efficacy	Early (<4y) diffuse SSc plus visceral involvement *or* progressive interstitial lung disease	34	TBI 800 cGy + CY 120 mg/kg + 90 mg/kg eATG CD34+ selected graft	64% at 5y	15% (4/26) at 5y	23% (8/34)	64% at 5y
USA (Chicago)/2007[96]	Phase I	None, single arm	Safety (toxicity and transplant-related mortality)	Diffuse SSc plus visceral involvement *or* pulmonary disease regardless of skin involvement	10	CY 200 mg/kg + 7.5 mg/kg rATG Unselected graft	70% at mean 25.5 months	22% (2/9) at mean 25.5 months	Zero	90% at mean 25.5 months

Table 3 – *(Continued)*

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria	N	Transplant regimen	PFS	Relapse/ progression rate	Non-relapse mortality	OS
Germany (Berlin)/2012[12]	Retrospective analysis	None, single arm	Safety and efficacy	CY inefficacy *or* diffuse SSc with bad prognosis	26	CY 200 mg/kg + 40 mg/kg rATG* CD34+ selected graft	53% at 3y	39% (9/23) at 3y	4% (1/26)	74% at 3y
EUA (Chicago) and Brazil (Ribeirão Preto)/2013[89]	Retrospective analysis	None, single arm	Efficacy and use of cardiac screening	Diffuse SSc plus visceral involvement *or* pulmonary disease regardless of skin involvement	90	CY 200 mg/kg + 4.5-6.5 mg/kg rATG No graft selection	70% at 5y	15% (13/85) at 5y	6% (5/90)	78% at 5y
Italy (Milan)/2017[11]	Phase II	HSCT vs historical cohort	Safety and efficacy	Diffuse SSc with progression of skin or of visceral disease	18 HSCT + 36 SSc controls	CY 200 mg/kg + 7.5 mg/kg rATG CD34+ selected graft	Not available. Significantly higher PFS in HSCT than in SSc control group	Not available. Significantly lower disease progression in HSCT than in SSc control group	5.6% (1/18) in HSCT group. Not available for SSc control group	89% in HSCT group and 39% in SSc controls, at 5y
Europe (multicenter) and Brazil (Ribeirão Preto)/2020[102]	Prospective observational	None, single group	Safety and efficacy	Transplanted patients with progressive SSc with data registered to the EBMT database	80	In 76 patients: median CY 200 mg/kg + rATG In 4 patients: Thiotepa 10 mg/kg + CY 100 mg/kg + rATG CD34+ selection in 44%	82% at 2y	13% (11/85) in 2y	6.25% (5/80)	90% in 2y

Table 3 – (*Continued*)

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria	N	Transplant regimen	PFS	Relapse/ progression rate	Non-relapse mortality	OS
Randomized studies										
ASSIST (Chicago, USA)/2011[99]	Phase II, open label, randomized 1:1 Patient cross-over from CY to HSCT arm allowed at 12 months of FU.	HSCT versus 6 monthly IV CY pulses	Improvement in skin score or lung function in 12 months of follow-up	Diffuse SSc plus visceral involvement *or* progressive interstitial lung disease	19 (10 HSCT arm and 9 CY arm)	CY 200 mg/kg + 6.5 mg/kg rATG Unselected graft	100% in HSCT arm (10 patients) and 11% in CY arm, at 12 months FU. 7 patients from CY arm crossed over to HSCT at 12 months FU and all improved. At 2.6y of mean FU after HSCT, PFS was 88%	Zero in HSCT arm and 89% (8/9) in CY arm at 12 months of FU. 12% (2/17) in all transplanted patients (original and crossed-over) at mean 2.6y of FU	Zero in HSCT and CY arms, at mean 2.6y of FU	100% at mean 2.6y of FU
ASTIS (Europe multicenter)/2014[88]	Phase III, open label, randomized 1:1	HSCT versus 12 monthly CY pulses	Progression/ relapse-free survival, toxicity, efficacy.	Early (<4y) diffuse SSc plus major organ involvement *or* progressive diffuse skin disease (<2y) with no visceral involvement	156 (79 HSCT arm and 77 CY arm)	CY 200 mg/kg + 7.5 mg/kg rATG CD34+ selected graft	77% in HSCT arm and 65% in CY arm, at 4y FY	11% (7/66) in HSCT arm and 35% (20/57) in CY arm at 4y FU	10% (8/79) in HSCT arm and zero in CY arm at 4y FU	80% in HSCT arm and 65% in CY arm at 4y FU
SCOT (USA multicenter)/2018[100]	Phase II, open label, randomized 1:1	HSCT versus 12 monthly CY pulses	Global rank composite score at 54 months of FU	Any form of early SSc (<5y) plus interstitial lung disease *or* previous scleroderma renal crisis	55 (33 HSCT arm and 32 CY rm)	TBI 800 cGy + CY 120 mg/kg + 90 mg/kg eATG CD34+ selected graft	74% in HSCT arm and 47% in CY arm, at 72 months FU	18% (6/33) in HSCT arm and 41% (14/34) in CY arm, at 54 months FU	6% (2/33) in HSCT arm. Zero in the CY group	86% in HSCT arm and 51% in CY arm, at 72 months FU

PFS: progression-free survival; OS: overall survival; *N*: number of enrolled subjects; USA: United States of America; y: years; SSc: systemic sclerosis; TBI: total body irradiation; IV CY: intravenous cyclophosphamide; eATG: equine anti-thymoglobulin; rATG: rabbit anti-thymoglobulin; FU: follow-up; HSCT: hematopoietic stem cell transplantation; rATG*: this center used ATG-Fresenius (Neovii-Biotech, Germany).

(EBMT) compared SSc patients transplanted with or without graft selection, showing similar clinical outcomes.[101] Although not statistically significant, patients who received unselected grafts tended to have better overall and disease-free survival than patients treated with selected grafts. More recently, a second prospective observational study from the EBMT reported, conversely, higher disease improvement rates after HSCT with CD34+ graft selection, although there was no impact on the progression-free survival.[102] A third, smaller, recent study has also shown better outcomes in patients transplanted with selected versus non-selected grafts (Table 3).[103] In summary, the question shall not be settled without a prospective randomized trial.

Most transplant centers adopt non-myeloablative conditioning regimens, however a group of North American multicenter investigators, from 26 transplant sites, has consistently reported their experience with myeloablative protocols including full body irradiation.[95,104] In this scenario, the most recently published randomized trial (SCOT trial) has shown good results in the myeloablative transplant group (Table 3).[100]

The experience with allogeneic transplantation for systemic sclerosis is limited to isolated case reports.[14,105,106] Therefore, clinical evidence is insufficient to recommend this treatment modality for patients with SSc.

Guidelines for transplantation in systemic sclerosis

The three randomized studies already published provide solid evidence to recommend autologous hematopoietic stem cell transplantation for severe and progressive cases of systemic sclerosis. According to the Oxford Center for Evidence-Based Medicine's evidence table,[107] we consider the evidence to have Grade A and Level 1B. Patients should be thoroughly evaluated for heart dysfunction and fibrosis before transplantation and the procedure should be performed in centers with experience in managing patients with systemic sclerosis during transplantation.

Crohn's disease

Crohn's disease is a chronic relapse-remitting inflammatory bowel disorder that can affect any site of the digestive tract.[108] Currently, Crohn's is a global disease, with increasing worldwide incidence and prevalence.[109] In Brazil, the prevalence of Crohn's disease varies according to the region of the country, from 12.8/100,000 in the Northeastern area, to 14.1 and 24.3/100,000 in the states of Espírito Santo and São Paulo, respectively.[110–112]

The disease is immunologically mediated and heterogeneous among the affected patients. The imbalanced and dysregulated immunity of the intestinal mucosa provides an inappropriate response against original intestinal flora or luminal antigens. These responses are responsible for the symptoms and the intestinal lesions observed in Crohn's disease. Disturbances in the intestinal mucosa occur in patients genetically predisposed and exposed to environmental triggers.[113]

The mucosal disturbance may be linked to abnormalities in the toll-like recognition receptors (TLRs), which play an essential role in the pathogenesis of numerous autoimmune diseases. The perturbation of the TLR signaling pathway in intestinal macrophages has been associated with tolerance breakdown in autoimmune diseases.[114] Patients with Crohn's disease present defects in the innate immune pathway, and inadequate T cell responses to pathogenic mutations in the nucleotide-binding oligomerization domain 2 (NOD2) and autophagy-related protein 16-1 (ATG16L1) genes that impair bacterial sensing and clearing.[108] Imbalances between natural (nTreg) and induced regulatory T-cells (iTreg), and effector T-helper (Th) cells (Th1/Th17) that defend the mucosa from bacteria, fungi and viruses are associated with Crohn's disease.[108,115] The Genoma Wide Association Study Project identified 71 susceptibility loci on 17 chromosomes and regions related to inflammatory bowel disease, renamed IBD1 to IBD9.[116]

The age at diagnosis, disease location and behavior along the gastrointestinal tract are defined according to Montreal classification.[117] The cardinal symptoms of Crohn's disease include abdominal pain, diarrhea, hematochezia, bloody stools, fatigue, weight loss, fever, recurrent fistulas, and extraintestinal manifestations.[118] Extraintestinal manifestations are common, such as arthropathy (both axial and peripheral), ocular involvement (uveitis, scleritis, and episcleritis), dermatological (including pyoderma gangrenosum and erythema nodosum), nephrolithiasis, hepatobiliary involvement (primary sclerosing cholangitis), cholelithiasis, venous or arterial thromboembolism, and other associated immune-mediated diseases.[119]

The majority of patients (80%) present small bowel involvement, 1/3 only ileitis, 1/3 ileocolonic involvement and in 1/3, Crohn's disease is restricted to the colon and rectum. In a North American cohort, 30% of patients presented perianal disease, while in Europe this complication was detected in only 9% of patients.[120] Oral and gastroduodenal involvement is estimated in approximately 10% of Crohn's disease patients.[120] Fistulas are common: enteric, cutaneous, vesical, vaginal, anal, or rectal. Complications in the involved organs, such as abdominal masses and abscesses, are frequent, with perianal fistulizing disease in up to one-quarter of the patients.[119] At diagnosis, most (71%) patients present a non-stricturing and non-penetrating profile of disease, but 21% have a stricturing and 8% a penetrating behavior.[120]

Surgery due to intestinal inflammation or related complications, such as stenosis, fistulas or perforations, occurs in 13% of patients in the first year of diagnosis, and 22% in five years of follow-up. The 10-year cumulative risk of major abdominal surgery is of approximately 55%.[108,109,119,120]

Diagnosis of Crohn's disease is based on the combination of a history of chronic intestinal inflammation symptoms and colonoscopy, magnetic resonance enterography and histopathological findings.[119] Routine laboratory studies include complete blood count, basic metabolic panel, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver function tests, iron distribution studies, vitamin B12 and D levels, β2 microglobulin and an immunologic panel study.[121]

Ileocolonoscopy and biopsy are considered gold standard tools for diagnosis of Crohn's disease. When visualizing the ileum, right, transverse and left colon, abnormalities in the rectum mucosa and lesions are observed as cobblestones, with

Table 4 – Results of Crohn's disease study outcomes.

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria	N	Transplant regimen	PFS	Relapse/ progression rate	Non-relapse mortality	OS
Single-arm studies										
Italy (Milan) 2007[136]	Phase I/II Prospective	None, single arm	Safety and clinical/endoscopic response	CDAI > 250 Active intestinal lesions Failed > 2 IS C-reactive protein > 1 mg/dL	4	CY 200 mg/kg + 7.5 mg/kg rATG Unselected graft	75% at 16.5 months mean FU	25% (1/4) at 16.5 months mean FU	Zero at 16.5 months	100% at 16.5 months
EUA (Chicago) 2010[4]	Phase I/II Prospective	None, single arm	Safety and clinical outcomes	CDAI > 250 Crohn's severity index > 16 Failed anti-TNF	24	CY 200 mg/kg + 6 mg/kg rATG *or* 90 mg/kg eATG CD34+ selected graft	19% at 5y	15/23 at mean FU of 4.4y	Zero TRM 1 accidental death at 3y	95% at 5y
Netherlands 2011[137]	Case series	None, single arm	None described	Active disease Failed anti-TNF Risk of resection surgery	3 (only 2 transplanted)	CY 200 mg/kg + 90 mg/kg eATG CD34+ selected graft	Zero at 5y (both patients relapsed at 3 and 12 m post-AHSCT	100% (2/2) at 5y	Zero	100% at 5y
Germany (Freiburg) 2012[138]	Phase I/II Prospective	None, single arm	Safety, feasibility and efficacy	Active disease Failed conventional therapy	12 (only 9 transplanted)	CY 200 mg/kg CD34+ selected graft	17% (2/12) at mean follow-up of 3.1y	78% (7/9) at 3.1y	Zero at mean 3.1y	100% at mean 3.1y
United Kingdom (3 centers) 2014[139]	Retrospective case series	None, single arm	Long-term clinical outcomes	Active disease failed conventional therapy	6	CY 200 mg/kg + 7.5 mg/kg rATG CD34+ selected graft in 2 patients	Zero (6/6 relapses)	100% at median 10 months after AHSCT	Zero	100% at median 87 months FU
Brazil (S. José do Rio Preto) 2017[142]	Phase I/II Prospective	None, single arm	Safety and early clinical outcomes (first 30 days after AHSCT)	CDAI > 150 Active intestinal lesions Risk of resection surgery Failed anti-TNF	14	CY 200 mg/kg + 6.5 mg/kg rATG Unselected graft	93% at 30 days	1/14 at 30 days	Zero at 30 days	100% at 30 days

Table 4 – (*Continued*)

Site/year of publication(ref)	Study design	Comparisons	Endpoints	Inclusion criteria	N	Transplant regimen	PFS	Relapse/ progression rate	Non-relapse mortality	OS
Europe multicenter (EBMT) 2018[143]	Retrospective survey	None, single arm	Safety and efficacy	Patients transplanted from 1997 to 2015 Excludes ASTIC patients	82	86% CY 200 mg/kg + ATG 11% CY 200 mg/kg + CD34 selection	54% at 1y 27% at 41 months	73% (60/81) at median 10 months after AHSCT	1.2% (1/82)	97% at 5y
Spain (Madrid) 2019[144]	Retrospective case series	None, single arm	Safety and efficacy	Patients with active Crohn's disease transplanted from 2011 to 2017.	7	CY 200 mg/kg + rATG (dose not described) Unselected graft	29% at 48 months	71% (5/7) at 48 months	Zero	100%
Randomized study										
ASTIC (EBMT, multicenter) 2016[140]	Phase II, open label, randomized 1:1	Patients randomized after mobilization to immediate AHSCT or control treatment with AHSCT deferred for 1y	Sustained clinical and endo-scopic/radiologic remission at 1 y	Active disease Impaired func-tion/quality of life Failed ≥3 IS/biologicals	45 (23 AHSCT and 22 control treatment)	CY 200 mg/kg + 7.5 mg/kg rATG Unselected graft	8.7% (2/23) in the AHSCT group 4.5% (1/22) in the control group	95% (20/21) in the AHSCT group at 1y 94% (16/17) in the control group at 1y	4.3% (1/23) at 1y in the transplant group Zero in the control group	96% at 1y in the transplant group 100% in the control group

PFS: progression-free survival; OS: overall survival; *N*: number of enrolled subjects; USA: United States of America; y: years; CDAI: Crohn's disease activity index; TRM: transplant-related mortality; IV CY: intravenous cyclophosphamide; eATG: equine anti-thymoglobulin; rATG: rabbit anti-thymoglobulin; FU: follow-up; HSCT: hematopoietic stem cell transplantation; anti-TNF: treatment with anti-tumor necrosis factor monoclonal antibody; IS: immunosuppressors; biologicals: biological agents.

nodularity, edema, superficial or deep ulcerations, friability, or stenosis. The Crohn's Disease Endoscopy Severity Index (CDEIS) and the Simple Endoscopy Score for Crohn's disease (SES-CD) were developed and validated to evaluate the compromised intestinal surface, and to characterize the severity of the involvement.[122,123] All lesions should be biopsied for histological study. Upper endoscopy should only be performed in patients with upper gastrointestinal signs and symptoms and wireless capsule endoscopy may be an option for patients without intestinal strictures.[119] Magnetic resonance enterography is a suitable method for the diagnosis, as the location, extension, disease activity, presence of obstructions, fistulas, and severity of inflammatory lesions of Crohn's disease need to be determined.[124]

Disease activity is measured by scores, such as the Crohn's Disease Activity Index (CDAI), and the Harvey Bradshaw index (HBi).[125,126] A CDAI below 150 is defined as disease remission. A HBi below five defines remission, 5–7 mildly active disease, 8–16 moderately active disease and higher than 16, severe disease.

Treatment aims to stabilize Crohn's disease, reduce symptoms, and heal intestinal lesions. Anti-inflammatory drugs, immunosuppressive agents, corticosteroids, and biological agents are prescribed alone or in combination. Drugs are usually administered in a stepwise sequence, named "up and down" treatment. In more severe cases, early indication of biological agents associated with immunosuppressants remain controversial and debated.[108]

Hematopoietic stem cell therapy

Hematopoietic stem cell transplantation (HSCT) has emerged as a potential treatment for Crohn's disease due to the chronicity of the disease and lack of further therapeutic options in refractory patients. Additionally, since 1993, there are several case reports in the literature of Crohn's disease patients with concomitant leukemia or lymphoma who improved from the former when transplanted for the latter.[127–132]

In 2003, investigators from the Northwestern University (Chicago, USA) published their successful experience with the first two patients treated with AHSCT for Crohn's disease as primary indication.[133,134] A subsequent update from the same investigators described dramatic clinical remissions in 11 from a total of 12 transplanted patients, in 18 months of follow-up.[135] In 2010, a last update described the long-term follow-up of 24 Crohn's disease patients transplanted in Chicago, showing high rates of disease progression over a five-year follow-up (Table 4).[4]

The European centers also reproduced the North-American protocol, with similar outcomes of low toxicity and high rates of short-term disease remission.[136] Longer follow-up, however, confirmed the high relapse/progression rates.[137–144] A European multicenter randomized study (Autologous Stem Cell Transplantation in Refractory Crohn's Disease, ASTIC) had a very strict study design and ambitious endpoints, and thus failed to show superiority of AHSCT versus mobilization only (Table 4).[140] A later reassessment of the same results, with more traditional endpoints, enabled more optimistic conclusions; that AHSCT promotes clinical and endoscopic benefits, despite a high burden of adverse events.[145] To date, the EBMT registry reports Crohn's disease as the third most frequent autoimmune disease indication for AHSCT.[141]

In Brazil, the first report of AHSCT for Crohn's disease was published in 2013.[142] To date, at least 57 procedures have been performed in four Brazilian centers (unpublished data). A single institution Brazilian trial enrolled 14 Crohn's disease patients for AHSCT with high rate of disease remissions and improved quality of life at 30 days post-transplantation (Table 4).[146] Longer follow-up of the quality of life in these patients, evaluated by the IBDQ (Inflammatory Bowel Disease Questionnaire) and SF-36 (Short Form-36) questionnaires show sustained benefit at four years post-AHSCT (data not published).

The field of AHSCT for Crohn's disease has advanced over time, in parallel to the learning curve in other autoimmune disease indications. Patient selection and disease stratification are important steps that precede AHSCT, and aim to improve safety and post-transplantation outcomes.[46,143] Perianal disease, fistulas and intra-abdominal abscesses, as well as presence of ostomies, are not considered absolute exclusion criteria, but increase risks associated to the procedure and should be carefully considered before patient enrollment. Moreover, hematopoietic progenitor cells may be successfully and safely mobilized from the peripheral blood with low (2 g/m^2) doses of cyclophosphamide.[147] Disease reactivation over time is still high (Table 4) and whether CD34+ graft selection has any effect on long-term control remains to be defined.[4,136–140,142,143] Finally, there is evidence to suggest that after AHSCT, patients become more responsive to conventional therapy than before the procedure.[140,141] These aspects should be explored in future studies.

The new ongoing protocols, ASTIC-Lite (ASTIC-low intensity therapy evaluation, EBMT), and the AutoCrohn2 (São José do Rio Preto, Brazil), include a more refined patient assessment and stratification with accurate clinical, immunological, magnetic resonance and microbiota studies. These studies aim for a better understanding of the therapeutic potential of AHSCT for patients with Crohn's disease.[147–149]

Guidelines for transplantation in Crohn's disease

Autologous HSCT has the potential to induce clinical remission and improve quality of life in patients with Crohn's disease with poor prognosis or that are refractory to immunosuppressants or biologic agents. AHSCT is considered safe, but associated with a high number of adverse events, mainly infectious. Therefore, AHSCT for Crohn's disease should be performed by experienced centers, with specialized teams to manage gastrointestinal and infectious complications. Early referral is recommended to optimize clinical outcomes and minimize risks.

Conclusions

Scientific evidence supports the clinical use of autologous hematopoietic stem cell transplantation (AHSCT) for multiple sclerosis (MS), systemic sclerosis and Crohn's disease. In systemic sclerosis, AHSCT is indicated due to the severity of the disease and lack of therapeutic options, with effectiveness

confirmed by phase III randomized trials. In MS, treatment with AHSCT is supported by 25 years of research, including recent phase III trials comparing transplant to new drugs. In Crohn's disease refractory to treatment with immunosuppressor and biological agents, long-term benefits have been shown after AHSCT, despite low rates of sustained disease remission.

The role of HSCT in these and in other autoimmune diseases is likely to evolve further with increased clinical experience, especially with regards to optimal timing of transplant. It is expected that improvements in design of clinical trials and experimental studies further expand the impact of HSCT in this field.

Conflicts of interest

The authors declare no conflicts of interest.

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