Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: BMT- Hematopoietic Cell Transplantation for Autoimmune Diseases

Description/Background

Most patients with autoimmune disorders respond to conventional drug therapies; however, conventional drug therapies are not curative-and a proportion of patients suffer from autoimmune diseases that range from the severe to the recalcitrant to the rapidly progressive. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT).

AUTOIMMUNE DISEASE TREATMENT

Immune suppression is a common treatment strategy for many autoimmune diseases, particularly the rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, scleroderma). Most patients with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressant's and immunomodulating drugs; however, conventional drug therapies are not curative, and a proportion of patients suffer from autoimmune diseases that range from severe to recalcitrant to rapidly progressive. It is for this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT). The primary concept underlying use of HCT for these diseases is that ablating and "resetting" the immune system can alter the disease process, by inducing a sustained remission that possibly leads to cure.(1)

Hematopoietic Cell Transplantation (HCT)

The rationale in using HSCT in autoimmune diseases is to 'reset' one's immune system by purging the existing immune system and regenerating a new and healthy repertoire of immune cells .Several factors may contribute to the resetting and regulation of the immunological clock. Lymphotoxic chemotherapy leads to a profound and persistent lymphopenia and reduced levels of putative pathogenic antibodies. This 'reset' of the immunological clock could underlie the prolonged clinical remissions in some patients. However, relapses are possible which may be

due to persistence of autoreactive memory cells or incomplete immunologic renewal and regulation.

There is growing evidence that autologous HSCT can re-establish immunological tolerance by:

- activating thymopoiesis and establishing a diversified T cell receptor repertoire
- increasing the number of regulatory T cells which are important in the preservation of tolerance
- ATG targeting long-living, antibody-producing plasma cells by complement-mediated lysis and apoptosis This 'reset' of the immunological clock could underlie the prolonged clinical remissions in some patients.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic or molecular techniques. The term HLA refers to the tissue type expressed at the HLA-A, -B, and –DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANTATION

Myeloablative (Conventional) Conditioning

The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host-disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow with presumably normal hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT

Reduced-intensity conditioning (RIC), sometimes referred to as non-myeloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA is variable, with numerous versions employed, all regimens

seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC/NMA is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism.

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Medical Policy Statement

Autologous hematopoietic cell transplantation may be considered a useful therapeutic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:
Autologous hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma when **ALL** of the following are met:

- Condition is rapidly progressing, and the prognosis is poor
- Internal organ involvement is indicated by one of the following:
  - Cardiac involvement (ex. abnormal electrocardiogram)
  - Pulmonary (**BOTH** of the following):
    - Evidence of interstitial lung disease (one of the following):
      - Pulmonary fibrosis
      - Ground glass appearance on high resolution chest CT
    - Diffusing capacity of carbon monoxide (DLCo) < 80% of predicted value **OR** a decline of forced vital capacity (FVC) of ≥ 10% in last 12 months
  - Renal: scleroderma-related renal disease

Autologous hematopoietic cell transplantation as a treatment for *relapsing-remitting*[a] multiple sclerosis (MS) when **ALL** of the following are met:

- Disease is resistant to treatment with 1 or more disease modifying therapies (i.e., alemtuzumab, fingolimod, natalizumab, or other highly effective medication)
- Ongoing disease activity, measured either by clinical relapses or new MRI-detected lesions (including unequivocally new T2 or new gadolinium-enhanced lesions) *when medication adherence has been maintained* and **one** of the following are met:
  - Increased disability on examination over a 1-year period of time

- One or more relapses within a 1-year period of time
- Expanded Disability Status Scale score of 2.0 to 6.0
- Adults 18 years of age and older[b]
- Adult disease onset occurred within last 10 years; **OR** if diagnosed as a child, onset is within the last 15 years.

[a]Relapsing-remitting multiple sclerosis is the most common type of multiple sclerosis (MS) and is characterized by episodes of neurological symptoms (relapses) followed by periods of partial or complete recovery (remissions).

[b]Age should be reviewed in context with risk-benefit analysis that takes into account disability status and duration of disease. A lower regenerative capacity of the nervous system, aging of the immune and nervous systems, comorbidities, and the risk of other comorbidities argue against autologous hematopoietic stem cell transplantation in persons with MS beyond 50 years. In older age, a short disease duration and high inflammatory activity are a pre-requisite to consider autologous hematopoietic stem cell transplantation.

Exclusions:

- Treatment of systemic sclerosis (scleroderma):
  - In severe organ involvement that is irreversible
  - Not meeting the above inclusion criteria
- Treatment of multiple sclerosis not meeting criteria listed above
- Autologous or allogeneic hematopoietic cell transplantation as a treatment of autoimmune diseases not listed above, including, but not limited to:
  - Systemic lupus erythematosus
  - Juvenile idiopathic and rheumatoid arthritis
  - Chronic inflammatory demyelinating polyneuropathy
  - Type 1 diabetes mellitus
  - Crohn's disease
  - Immune cytopenia
  - Relapsing polychondritis

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes: *(for Autologous transplant)*

38206	38207	38208	38211	38212	38213
38214	38215	38232	38241	38243	

Other codes (investigational, not medically necessary, etc.)

38204	38205	38209	38210	38230	38240
38242	81267	81268	81370	81271	81372
81373	81374	81375	81376	81377	81378
81379	81380	81381	81382	81383	86812
86813	86816	86817	86821	S2140	S2142
S2150					

POTENTIAL CONTRAINDICATIONS FOR TRANSPLANT:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that ***attending staff at the transplant center have considered all contraindications*** as part of their overall evaluation of potential organ transplant recipient ***and have decided to proceed.***

Rationale

AUTOIMMUNE DISEASES

Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including multiple sclerosis, systemic sclerosis/scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and chronic immune demyelinating polyneuropathy. The National Institutes of Health has estimated that 5% to 8% of Americans have an autoimmune disorder.

The goal of autologous HCT in individuals with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablation) and generate new, self-tolerant lymphocytes. While evidence for the use of allo-HCT for autoimmune diseases is currently limited, the goal is to possibly eliminate genetic susceptibility to the autoimmune disease, potentially resulting in a cure.

Recent reviews have summarized the research to date using HCT to treat a number of autoimmune diseases.(2,3)

In March 2009, individuals with an autoimmune disease who had undergone HCT were registered in the European Group for Blood and Marrow Transplantation (EBMT)/European League Against Rheumatism database. The database included 1031 individuals with the clinical indications of multiple sclerosis (MS; n=379), systemic sclerosis (n=207), systemic lupus erythematosus (SLE; n=92), rheumatoid arthritis (RA; n=88), juvenile idiopathic arthritis (JIA; n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn disease (n=23).(3)

Clinical Context and Therapy Purpose

The purpose of hematopoietic cell transplantation (HCT) in individuals who have autoimmune disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with autoimmune diseases, specifically:

- multiple sclerosis
- systemic sclerosis/scleroderma
- systemic lupus erythematosus
- juvenile idiopathic or rheumatoid arthritis
- chronic inflammatory demyelinating polyneuropathy
- type 1 diabetes
- other autoimmune diseases such as Crohn's disease, immune cytopenias, and relapsing polychondritis.

Interventions
The therapy being considered is HCT.

HCT is performed in a tertiary care center by transplant specialist teams.

Comparators
Comparators consist of conventional medical therapy. Most individuals with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressants, and immunomodulating drugs; however, conventional drug therapies are not curative, and a proportion of individuals suffer from autoimmune diseases that range from severe to recalcitrant to rapidly progressive.

Outcomes
The general outcomes of interest are overall survival, health status measures, QOL, treatment-related mortality, and treatment related morbidity. Specific outcomes of interest include progression-free survival, improvement in clinical symptoms, and adverse events.

Follow-up for 1 year is standard to measure treatment-related adverse events and mortality. Several years of follow-up are necessary to determine the efficacy of treatment.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
- To assess longer term outcomes and adverse effects, single-arm studies that capture longer periods of follow up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

MULTIPLE SCLEROSIS

Systematic Reviews

Characteristics of systematic reviews are presented in Table 1 and results of systematic reviews are presented in Table 2.

A systematic review by Reston et al (2011) evaluated the safety and efficacy of autologous HCT in patients with progressive MS refractory to conventional medical treatment (Table 1).(4) Fourteen studies met inclusion criteria, of which 8 case series met the inclusion criteria for the primary outcome of progression-free survival (PFS) with a median follow-up of at least 2 years. The other 6 studies were included for a summary of mortality and morbidity rates. Across the 8-case series, there was substantial heterogeneity. Most patients (77%) had secondary progressive MS, although studies also included patients with primary progressive, progressive-relapsing, and relapsing-remitting MS (RRMS).

Sormani et al (2017) conducted a systematic review and meta-analysis on the use of autologous HCT for the treatment of patients with severe treatment-refractory MS.(5) The studies differed in types and intensities of conditioning regimens used before HCT: low (n=2), intermediate (n=7), high (n=4), and mixed (n=2). Quality assessment of included studies was not discussed. Rate of progression at 2 and 5 years were calculated, as well as treatment-related and overall mortality. The pooled proportion of patients with no evidence of disease activity at 2 years was 83% (range 70% to 92%) and at 5 years was 67% (range 59% to 70%).

Ge et al (2019) reported a systematic review and meta-analysis to assess progression-free survival (PFS) and disease activity-free survival, as well as transplant-related mortality (TRM) and overall deaths, after autologous HCT for MS.(6) The authors identified 18 eligible studies with a total of 732 participants. Pooled estimated PFS was 75%. Low- and intermediate-intensity treatments had higher PFS than high-intensity treatments. In addition, relapsing remitting MS benefited from autologous HCT more than other MS subtypes. Patients with gadolinium-enhancing (Gd+) lesions at baseline responded better to autologous HCT. Overall, 9 transplant-related deaths occurred, and estimated TRM was greater with the use of high-intensity treatment regimens and in studies conducted before 2006. Twenty-seven patients died during follow-up, primarily of infection or pneumonia. Several limitations of the meta-analysis include possible publication bias, a lack of RCTs, and differences in autologous HCT procedures, patient characteristics, and duration of follow-up across studies.

Nabizadeh et al (2022) conducted a systematic review and meta-analysis on the use of autologous HCT in patients with MS.(7) Fifty studies, including 7 RCTs, with a total of 4831 patients were included. The pooled estimated PFS was 73% (95% confidence interval [CI], 69% to 77%; I^2= 89.89%). There was a significant decrease in Expanded Disability Status Scale (EDSS) score aftertreatment (standardized mean difference [SMD], -0.48; 95% CI, -0.75 to -0.22), and the annualized relapse rate (ARR) was decreased relative to the pretreatment period (SMD, -1.58; 95% CI, -2.34 to -0.78). However, the analysis found a higher incidence of TRM after autologous HCT versus other disease-modifying therapies when evaluating long-term outcome measures; the analysis considered an endpoint of all TRM at the end of a 5-year follow-up duration. Limitations of the meta-analysis include possible publication bias, minimal number of RCTs, lack of studies focusing on specific subtypes of MS, high heterogeneity between included studies, and unspecified duration of follow-up across studies.

Table 1. Characteristics of Meta-Analyses on the Use of Autologous HCT for Multiple Sclerosis

Study	Dates	Studies	Participants	N (range)	Follow-up

Reston (2011)	Through Feb 2009	1 database 13 cohort	Patients with progressive and treatment-refractory multiple sclerosis	428 (5 to 169)	Median: 24 months
Sormani (2017)	1995 to 2016	1 RCT 14 cohort	Patients with severe and treatment-refractory multiple sclerosis	764 (7 to 178)	Median: 42 months
Ge (2019)	Through 2017	18 uncontrolled observational studies	Patients with severe and refractory multiple sclerosis	732 (14 to 145)	Median: 48 months
Nabizadeh (2022)	Through Feb 2022	7 RCT 1 case series 42 cohort	Patients with MS	4831 (12 to 617)	NR

HCT: hematopoietic cell transplantation; NR: not reported; RCT: randomized controlled trial

Table 2. Results of Meta-Analyses on the Use of Autologous HCT for Multiple Sclerosis

Study	**N**	**Median Follow-up**	**PFS, % (95% CI)**	**Sub-population**	**N**	**TRM, N (%)**	**Non-TRM, N (%)**
Reston (2011)							
Intermediate-intensity conditioning	102	39 months	79.4 (69.9 to 86.5)	Cohort studies	259	7 (2.7)	6 (2.3)
High-intensity conditioning	61	24 months	44.6 (26.5 to 64.3)	Database	169	9 (5.3)	6 (3.5)
GE (2019)	**N**	**Median follow-up**	**PFS, % (95% CI)**	**DAF, % (95% CI)**		**TRM, % (95% CI)**	**OM, % (95% CI)**
Overall	732	48 months	75 (69 to 81)	61 (53 to 69)		1.34 (0.39 to 2.30)	3.58 (2.30 to 4.86)
Pts with RRMS			85 (77 to 92)				
Pts with GD+ lesions			77 (61% to 94%)				
Pts with Gd- lesions			47 (33 to 62)				
Low- and intermediate- intensity conditioning			80 (75 to 85)			0.97 (-0.05 to 1.98)	
High-intensity conditioning			58 (40 to 75)			3.13 (1.18 to 5.08)	
Sormani (2017)	**N**	**2-Year PR, % (95% CI)**	**N**	**5-Year PR, % (95% CI)**	**N**	**Pooled TRM,[a] % (95% CI)**	**OM[b] %, (95% CI)**
	764	17.1 (9.7 to 24.5)	679	23.3 (14.8 to 43.0)	764	2.1 (1.3 to 3.4)	1.0 (0.7 to 1.5)
Nabizadeh (2022)	N	PFS, % (95% CI)	EDSS score change, SMD (95% CI)	ARR change, SMD (95% CI)	EFS, % (95% CI)	OS, % (95%CI)	No evidence of disease activity, % (95%CI)
	4831	73 (69 to 77)	-0.48 (-0.75 to-0.22)	-1.58 (-2.34 to-0.78)	63 (54 to 73) 94	94 (91 to 96)	68 (59 to 77)

ARR: annualized relapse rate; CI: confidence interval; DAFS: disease activity–free survival; EDSS: Expanded Disability Status Scale; EFS: event-free survival; Gd+: gadolinium-enhancing; HCT: hematopoietic cell transplantation; MS: multiple sclerosis; NR: not reported; OM: overall mortality; PFS: progression free survival; PR: progression rate; Pts: patients; RRMS: relapsing remitting multiple sclerosis; SMD: standardized mean difference; TRM: treatment-related
[a]pooled TRM defined as number of deaths within 100 days of transplant/number of transplants
[b]OM defined as total number of deaths/number of patient years

Randomized Controlled Trials

A few notable RCTs are included here for review. An RCT, Autologous Stem Cell Transplantation in Multiple Sclerosis, which compared HCT with mitoxantrone for treatment of MS was published by Mancardi et al (2015).(9) Due to low patient enrollment, this trial's protocol, initially designed as a phase 3 study evaluating disability progression, was amended to a phase 2 study with a new primary outcome of disease activity, as measured by the number of new T2 magnetic resonance imaging (MRI) lesions in the four years post-treatment. Eligibility for the trial was secondary progressive or relapsing-remitting multiple sclerosis (RRMS), a documented worsening of symptoms during the last year, and lack of response to conventional therapy. Twenty-one patients were randomized to autologous HCT (n=9) or medical therapy (mitoxantrone) (n=12). Follow-up data were collected every 6 months for 48 months. Data were not available for 4 patients; missing data were imputed in the intention-to-treat analysis of the primary outcome. The median number of new T2 MRI lesions was 2.5 in the HCT group and 8 in the conventional therapy group (rate ratio, 0.21; 95% confidence interval, 0.10 to 0.48, p<0.001). Among secondary outcomes, the annualized relapse rate was significantly lower in the HCT group (19%) compared with the conventional therapy group (60%) (p<0.03). There was no statistically significant difference between groups in the rate of disease progression (defined as increase of > 1 point in Expanded Disability Status Scale [EDSS] score if baseline was 3.5 to 5.5 or increase of >0.5 if baseline 5.5 to 6.5) or change in disability status.

Burt et al (2019) reported a randomized controlled trial of nonmyeloablative HCT compared to continued disease-modifying therapy (DMT) on disease progression for patients with relapsing-remitting MS (RRMS).(10) Between 2005 and 2016, with final follow-up in 2018, 110 patients with relapsing remitting multiple sclerosis (RRMS) were randomized to receive HCT plus cyclophosphamide and antithymocyte globulin (n = 55) or DMT of higher efficacy or a different class than DMT taken in the previous year (n = 55). To be eligible, the participants had to have at least 2 relapses with DMT in the prior year and an Expanded Disability Status Score (EDSS) of 2.0 to 6.0 (EDSS score range 0–10, with 10 being the worst neurological disability). The primary end point of the study was disease progression, defined as an EDSS score increase of ≥1.0 point (minimally clinically important difference, 0.5) after ≥1 year on 2 evaluations 6 months apart. Three patients in the HCT group and 34 patients in the DMT group experienced disease progression, with a median follow-up of 2 years (mean = 2.8 years). Too few events in the HCT group prevented calculation of time to progression, but it was 24 months (interquartile range = 18–48 months) in the DMT group (hazard ratio [HR] = 0.07; 95% CI: 0.02–0.24). For the HCT group, the proportion of patients with disease progression was 1.92% (95% CI: 0.27%– 12.9%) at 1-year and 2-years, and by 4- and 5-years it was 9.71% (95% CI: 3.0%–28.8%). Disease progression for the DMT group was 24.5% (95% CI: 14.7%–39.1%) at 1 year, and 75.3% (95% CI: 60.4%–87.8%) by year 5. In the HCT group, the mean EDSS score decreased from a baseline of 3.38 to 2.36 at 1 year. In the DMT group, mean EDSS score increased from 3.31 to 3.98 at 1 year. Between-group difference in change in scores was -1.7 (95% CI: -2.03 to -1.29; p <.001). The results of the study suggest nonmyeloablative HCT is superior to DMT in prolonging time to disease progression in patients with RRMS. Study

limitations included sample size, option to cross over from DMT to HCT mid-study and the exclusion of other chemotherapy drugs used in the DMT group.

Nonrandomized Studies

Select nonrandomized studies with at least 2 years of follow-up and more than 20 enrolled patients are described below.

Fassas et al (2011) reported on the long-term results of a single-center study that investigated the effect of HCT on the treatment of MS (Table 3).(11) Progression-free survival (PFS) and treatment-related mortality (TRM) are presented in Table 4. The median time to progression was 11 years (range, 0-22 years) for patients with active central nervous system disease and 2 years for patients without (range, 0-6 years). Improvements by 0.5 to 5.5 (median, 1) EDSS points were observed in 16 cases, lasting for a median of 2 years. In 9 of these patients, EDSS scores did not progress above baseline scores. Gadolinium-enhancing lesions were significantly reduced after mobilization but were maximally and persistently diminished post-HCT.

Shevchenko et al (2012) reported on the results of a prospective, open-label, single-center study that analyzed the safety and efficacy of autologous HCT with reduced-intensity conditioning regimen with different types of MS (Tables 3 and 4).(12) Patients underwent early, conventional, and salvage/late transplantation. Efficacy was evaluated based on clinical and quality-of-life (QOL) outcomes. All patients, except 1, responded to treatment. At long-term follow-up (mean, 46 months), the overall clinical response in terms of disease improvement or stabilization was 80%. The estimated PFS rate at 5 years was 92% in the group after early transplant and 73% in the group after conventional/salvage transplant ($p=0.01$). No active, new, or enlarging lesions were found on MRI without disease progression. All patients who did not have disease progression did not receive therapy during the post-transplantation period. HCT was accompanied by a significant improvement in QOL, with statistically significant changes in most QOL parameters ($p<0.05$). A subsequent 2015 publication reported on 64 patients participating in this trial who had at least 36 months of follow-up (median, 62 months).(13) (Another 35 patients had shorter follow-up and the remainder were lost to follow-up.) Thirty (47%) of the 64 patients improved by at least 0.5 point on the EDSS score compared with baseline. Among the other patients, 29 (45%) were stable and 5 (7%) experienced worsening disease.

Mancardi et al (2012) reported on 74 consecutive patients with MS treated with autologous HCT following an intermediate-intensity conditioning regimen during the period from 1996 to 2008 (Table 3).(14) Thirty-six patients had secondary progressive disease and 25 had RRMS. Clinical and MRI outcomes were reported (Table 4). The median follow-up was 48.3 months (range, 0.8-126 months). After 5 years, 66% of patients remained stable or improved. Among patients with a follow-up more than 1 year, 8 (31%) of 25 subjects with RRMS had a 6- to 12-month confirmed EDSS score improvement more than one point after HCT compared with 1 (3%) of 36 patients with a secondary progressive disease course ($p=0.009$). Among the 18 cases with a follow-up more than seven years, 8 (44%) remained stable or had sustained improvement, while 10 (56%), after an initial period of stabilization or improvement (median duration, 3.5 years), showed a slow disability progression.

A single-center case series by Burt et al (2015) reported on 151 patients, 123 with RRMS and 28 with secondary progressive MS (Tables 3 and 4).(15) Patients were treated with non-

myeloablative HCT between 2003 and 2014. Six patients were not included in the outcomes analysis (lost to follow-up and non-reproducible neurologic findings). The remaining 145 patients were followed for a median of 2 years (range, 6 months to 5 years). Change in the EDSS score was the primary outcome. A decrease of at least 1.0 point was considered a significant improvement and an increase of at least 1.0 point was considered a significant progression. There was statistically significant improvement in EDSS score for the group as a whole compared with the pre-transplant mean score of 4.0, decreasing to a mean EDSS score of 2.5 at 3, 4, and 5 years. In post hoc analysis, patients most likely to have statistically significant improvements in EDSS scores were those with RRMS, with duration of disease of 10 years or less, and those without sustained fever during HCT.

A multicenter case series by Burman et al (2014) reported on 48 patients with aggressive RRMS (defined as disease with high relapse frequency, and who failed conventional therapy) (Tables 3 and 4).(16) Patients underwent autologous HCT. At the 5-year follow-up, relapse-free survival was 87% and the EDSS score progression-free survival (defined as a deterioration in EDSS score of <0.5 points) was 77%.

Atkins et al (2016) published a phase 2 trial investigating the use of immunoablation and autologous HCT for the treatment of aggressive MS (Table 3).(17) Inclusion criteria were: poor prognosis, ongoing disease activity, and EDSS score between 3.0 and 6.0. Twenty-four patients enrolled. PFS and TRM are presented in Table 4. During the extended follow-up period, without the use of disease-modifying drugs, no signs of central nervous system inflammation were detected clinically or radiologically. Clinical relapses did not occur among the 23 surviving patients in 179 patient-years of follow-up. Thirty-three percent of the patient's experienced grade 2 toxic effects and 58% experienced grade 1 transplantation related toxic effects.

Results from the High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) trial were published by Nash et al (2017) (Tables 3 and 4).(18) The trial evaluated 24 patients with MS who were treated with high-dose immunosuppression and autologous HCT. Outcomes were PFS (91%; 90% CI, 75% to 97%), clinical relapse-free survival (87%; 90% CI, 69% to 95%), and MRI activity-free survival (86%; 90% CI, 68% to 95%). Patients experienced high rates of adverse events: 92% had grade 3 and 100% had grade 4 adverse events. The majority of adverse events occurred between the start of conditioning to day 29 in the trial.

Muraro et al (2017) conducted a retrospective cohort study of patients with MS treated with HCT between 1995-2006 (Table 3).(19) Data was collected from 25 centers in 13 European countries. Results are presented in Table 4. Factors associated with neurological progression included age, progressive versus relapsing MS, and ≥ 2 previous therapies.

Kvistad et al (2019) performed a retrospective cohort study of 30 patients in Norway with relapsing/remitting MS treated with HCT between 2015-2018 (Table 3).(20) Results for PFS and TRM are presented in Table 4. Additionally, 13 (43%) patients experienced sustained improvement in EDSS score of 1 or more, and 25 patients (83%) experienced no evidence of disease activity.

Boffa et al (2021) performed a retrospective cohort study of 210 patients in Italy with relapsing/remitting, secondary progressive, or primary progressive MS treated with HCT

between 1997 and 2019 (Table 3).(21) Results for the primary outcome of disability worsening-free survival are presented in Table 4. Additionally, RFS at 5 and 10 years after transplant was 82.9% (95% CI, 76.6% to 89.2%) and 71.2% (95% CI, 61.8% to 80.6%), respectively.

Burt et al (2021) performed a retrospective cohort study of 414 patients with RRMS and 93 patients with newly diagnosed secondary-progressive MS treated with HCT at a single center in the US between 2003 and 2019. (Table 3).(22) Results for PFS and TRM are presented in Table 4. Additionally, RFS at 5 years for patients with RRMS and secondary-progressive MS was 80.1% and 98.1%,respectively.

Table 3. Characteristics of Observational Studies of HCT for MS (≥2 years Follow-Up)

Study	Study Design	Country	Participants	N	Median Years (range) follow-up
Fassas (2011)	Case series	Greece	Patients with aggressive MS treated with HCT	35	11 (2 to 15)
Shevchenko (2012) Shevchendo (2015)	Case series	Russia	Patients with relapsing/remitting or progressive MS treated with HCT	99	4 (NR)
Mancardi et al (2012)	Case series	Italy	Patients with severe MS treated with HCT	74	(0.8 to 10)
Burman (2014)	Case series	Sweden	Patients with aggressive MS	41	4 (1 to 9)
Burt (2015)	Case series	United States	Patients with relapsing/remitting	151	(0.5 to 5)
Atkins (2016)	Case series	Canada	Patients with relapsing MS	24	6.7 (4 to 13)
Nash (2017)	Case series	United States	Patients with relapsing/remitting or progressive MS treated with HCT	24	5.2 (1 to 6)
Muraro (2017)	Retrospective cohort	Europe (13 Countries)	Patients with aggressive treatment-refractory MS treated with HCT	281	6.6 (0.2 to 16)
Kvistad (2019)	Retrospective cohort	Norway	Patients with relapsing/remitting or progressive MS treated with HCT	30	26 (11 to 48)
Boffa (2021)	Retrospective cohort	Italy	Patients with relapsing/remitting, secondary progressive, or primary progressive MS treated with HCT	210	6.2 (NR)
Burt (2021)	Retrospective cohort	United States	Patients with relapsing/remitting or newly diagnosed secondary progressive MS treated with HCT	507	3 (NR)

HCT: hematopoietic cell transplantation; MS: multiple sclerosis. NR: not reported

Table 4. Results of Observational Studies of HCT for MS (≥2 years Follow-Up)

Study	Follow-up	PFS, % (95% CI)	TRM, N (%)
Fassas (2011)	15 years	All: 25 (NR) Active MRI lesions: 44 (NR)	2 (5.7%)
Shevchenko (2012) Shevchenko (2015)	8 years	80 (68 to 88)	0
Mancardi et al (2012)	4 years	NR	2 (2.7)
Burman (2014)	5 years	68 (NR)	0
Burt (2015)	2 years 4 years	92 (85 to 96) 87 (78 to 93)	0
Atkins (2016)	3 years	70 (47 to 84)	1 (4.2)
Nash (2017)	5 years	91 (75 to 97)	0
Muraro (2017)	5 year	All: 46 (42 to 54)	8 (2.8)

		Relapsing: 73 (57 to 88)	
Kvistad (2019)	2 years	7 (NR)	0
Boffa (2021)	5 and 10 years	5 years[a]: 79.5 (72.0 to 86.6); 10 years[a]: 65.5 (55.3 to 75.7)	3 (1.4)
Burt (2021)	4 years	RRMS: 95	

[a]This study measured disability worsening-free survival.
CI: confidence intervals; HCT: hematopoietic cell transplantation; MRI: magnetic resonance imaging; MS: multiple sclerosis; NR: not reported; PFS: progression-free survival; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary-progressive multiple sclerosis; TRM: treatment-related mortality.

Willison et al (2022) described the current literature regarding the use of HCT for the treatment of MS in terms of clinical trials, observational and retrospective studies, as well as immune reconstitution following transplantation, with a focus on the conditioning regimens used for transplantation. The evidence base predominantly consisted of non-randomised, uncontrolled clinical trials or data from retrospective or observational cohorts (n=2574), i.e. very few randomised or controlled trials. Fourteen trials used myeloablative conditioning regimens of either high (4 trials) or intermediate-intensity (10 trials) regimens and were either phase I, II or I/II. Included individuals who primarily had active disease with progression within the year prior to a HSCT and had trialed at least 1 DMT.

Section Summary: Multiple Sclerosis
Evidence for the use of HCT in individuals with MS consists of RCTs, systemic reviews, many single-arm studies and consensus guidelines. Several systematic reviews for HCT are available. Although large clinical trials and observational studies are not available regarding the efficacy of autologous HCT in multiple sclerosis, HCT/immune effector cell therapy (IECT) has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multi-center cohort studies. One RCT compared HCT (n=9) with mitoxantrone (n=12). The primary outcome was the number of new T2 lesions detected by MRI. The HCT group developed statistically fewer lesions than the mitoxantrone group. The other RCT compared nonmyeloablative HCT results in individuals with continued disease-modifying therapy and found a benefit to HCT in prolonging time to disease progression. Outcomes in the single-arm studies included PFS, relapse-free survival, disease activity-free survival, disability worsening-free survival, disease stabilization, number of new lesions, and improvements in EDSS scores. Improvements were seen in all outcomes compared with baseline. HCT/IECT can be considered as a treatment option for individuals after careful evaluation of risks and benefits. Consensus guidelines which consider the use of autologous HCT the standard of care in refractory multiple sclerosis are available. See Supplemental section below.

SYSTEMIC SCLEROSIS (SCLERODERMA)

Systematic Reviews
A review by Milanetti et al (2011) summarized 8 phase 1 and 2 clinical studies using autologous HCT to treat systemic sclerosis.(23) The number of patients in each study ranged from 6 to 57. The proportion of patients, across the studies, achieving a 25% decrease in the Rodnan Skin Score (RSS) ranged from 60% to 100%. Pooled analyses were not conducted.

Host et al (2017) conducted a systematic review of autologous HCT for the treatment of systemic sclerosis.(24) The literature search, conducted through March 2016, identified 9 studies (2 RCTs and 7 observational studies) for inclusion. The RCTs reported improvements in progression- and event-free survival and all studies reported improvements in modified

Rodnan Skin Score. However, TRM rates ranged from 0% to 23%, with higher rates found with higher doses of cyclophosphamide or myeloablative conditioning regimens. No pooled analysis was conducted.

Shouval et al (2018) conducted a meta-analysis of 4 studies (3 RCTs and 1 retrospective comparative study) on the use of autologous HCT compared with cyclophosphamide alone for the treatment of systemic sclerosis.(25) Quality assessment of the 3 RCTs found that 2 of the RCTs had low risk in the randomization methods and outcome reporting, 1 RCT was unclear in randomization methods, and all 3 were high risk since masking of patients and outcome assessors was not conducted. Meta-analyses of the RCTs showed that all-cause mortality favored HCT (risk ratio 0.6 [95% CI: 0.4 to 0.9]) and treatment related mortality favored cyclophosphamide alone (risk ratio 10.8 [95% CI: 1.4 to 85.7]).

Higashitani et al (2022) conducted a systematic review and meta-analysis of survival outcomes of HCT in patients with systemic sclerosis.(26) There were 22 studies included (3 RCTs; 19 observational cohorts). The pooled frequency of transplant-related death (N=700) was 6.30% (95% CI, 4.21 to 8.38). However, the authors note that the estimated frequency of treatment-related deaths has been declining over the last decade.

Bruera et al (2022) conducted a systematic review of autologous HCT for the treatment of systemic sclerosis.(27) There were 3RCTs (N=125) included (described below) with 3 different transplant modalities (non-myeloablative non-selective; non-myeloablative selective; myeloablative selective) and the comparator in all studies was cyclophosphamide. No study demonstrated an overall mortality benefit of autologous HCT when compared with cyclophosphamide; however, non-myeloablative selective HCT demonstrated OS benefits (using Kaplan-Meier curves) at 10 years and myeloablative selective HCT demonstrated OS benefits at 6 years. Event-free survival was improved with non-myeloablative selective HCT at 48 months(HR, 0.34; 95% CI, 0.16 to 0.74; moderate-certainty evidence) compared with cyclophosphamide; there was no improvement in EFS with myeloablative selective HCT at 54 months (HR, 0.54; 95% CI, 0.23 to 1.27; moderate-certainty evidence). All HCT transplant modalities reported improvement of mRSS compared with cyclophosphamide; however, there was low-certainty evidence that these modalities of HCT improved patient physical function.

Randomized Controlled Trials

An open-label, randomized, controlled phase II trial (ASSIST; Bert et al, 2011) evaluated the safety and efficacy of autologous non-myeloablative HCT compared with the standard of care cyclophosphamide (Table 5).(28) The primary outcome was improvement at 12 months, which was defined as a decrease in mRSS (<25% for those with initial mRSS >14) or an increase in forced vital capacity of more than 10% (Table 6). Patients in the control group with disease progression (>25% increase in mRSS or decrease of >10% in forced vital capacity) despite treatment with cyclophosphamide could switch to HCT 12 months after enrollment. Patients allocated to HCT (n=10) improved at or before 12-month follow-up, compared with none of the 9 patients allocated to cyclophosphamide (p<0.001). Treatment failure (i.e., disease progression without interval improvement), occurred in 8 of 9 controls, but did not occur in any of the 10 patients treated by HCT (p<0.001). After long-term follow-up (mean 2.6 years) of patients allocated to HCT, all but 2 patients had sustained improvement in mRSS and forced vital capacity, with the longest follow-up of 60 months. Seven patients allocated to receive cyclophosphamide switched treatment groups at a mean of 14 months after enrollment and underwent HCT without complication; all improved after HCT. Four of these patients followed

for at least 1 year had a mean (standard deviation [SD]) decrease in mRSS from 27 (SD=15.5) to 15 (SD=7.4), an increase in forced vital capacity from 65% (20.6) to 76% (26.5) and an increase in total lung capacity from 81% (14.0%) to 88% (13.9%). Data for 11 patients with follow-up of 2 years after HCT suggested that the improvements in mRSS ($p<0.001$) and forced vital capacity ($p<0.03$) persisted.

Results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published in June 2014 (Tables 5 and 6).(29) The ASTIS trial was a phase 3, randomized controlled trial (RCT) comparing autologous HCT with cyclophosphamide for the treatment of systemic scleroderma. A total of 156 patients were recruited between March 2001 and October 2009. Median follow-up was 5.8 years (interquartile range, 4.1-7.8 years). The primary end point was event-free survival, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney). Main secondary end points included treatment-related mortality, toxicity, and disease-related changes in mRSS, organ function, body weight, and quality-of-life scores. The internal validity (risk of bias) of ASTIS was assessed according to the U.S. Preventive Services Task Force criteria for randomized trials. The study was rated as "poor" quality according to this framework because of 2 flaws: outcome assessment was not masked to patients or assessors, and 18 (24%) of 75 patients in the control group discontinued intervention because of death, major organ failure, adverse events, or non-adherence. Furthermore, the trial design permitted crossover after the second year, but whether any patients did so and were analyzed as such is not mentioned. Finally, the authors reported that the use of unspecified concomitant medications or other supportive care measures were allowed at the discretion of the investigators, adding further uncertainty to the results. Of the 53 primary end point events recorded, 22 were in the HCT group (19 deaths, 3 irreversible organ failures; 8 patients died of treatment-related causes in the first year, 9 of disease progression, 1 of cerebrovascular disease, 1 of malignancy) and 31 in the control group (23 deaths, 8 irreversible organ failures [7 of whom died later]; 19 patients died of disease progression, 2 of cardiovascular disease, 5 of malignancy, 2 of other causes). The data show patients treated with HCT experienced more events in the first year but appeared to have better long-term event-free survival than the controls, with Kaplan-Meier curves for overall survival (OS) crossing at about 2 years after treatment with OS at that time estimated at 85%. According to data from the Kaplan-Meier curves, at 5 years, OS was an estimated 66% in the control group and about 80% the HCT group (p value unknown). Time-varying hazard ratios (modeled with treatment by time interaction) for event-free survival were 0.35 (95% CI, 0.15-0.74) at 2 years and 0.34 (95% CI, 0.16-0.74) at 4 years, supporting a benefit of HCT compared with pulsed cyclophosphamide. Severe or life-threatening grade 3 or 4 adverse events were reported in 51 (63%) of the HCT group compared with 30 (37% by intention-to-treat, $p=0.002$) of the control group.

Sullivan et al (2018) conducted an RCT comparing autologous HCT with cyclophosphamide for the treatment of scleroderma (SCOT - A Randomized, Open-Label, Phase II Multicenter Study of High-Dose Immunosuppressive Therapy Using Total Body Irradiation, Cyclophosphamide, ATGAM, and Autologous Transplantation With Auto-CD34+HPC Versus Intravenous Pulse Cyclophosphamide for the Treatment of Severe Systemic Sclerosis (SCSSc-01)) (Table 5).(30) The trial was originally designed for 226 patients, but due to low accrual, a total of 75 patients participated. Of the 36 patients randomized to receive HCT, 27 completed the trial per protocol (3 died and 6 withdrew prematurely). Of the 39 patients randomized to receive cyclophosphamide alone, 19 completed the trial per protocol (11 died and 9 withdrew

prematurely). The primary outcome was a global rank composite score. This score does not measure disease activity or severity but performs a pairwise comparison of the following: death, EFS, forced vital capacity (FVC), Disability Index of the Health Assessment Questionnaire, and the modified RSS. There were more percent pairwise comparisons favoring HCT over cyclophosphamide alone at 4- and 4.5-years follow-up (Table 6). The following disease progression events were significantly higher among patients receiving cyclophosphamide alone: initiating disease-modifying antirheumatic drugs, congestive heart failure leading to treatment, and pulmonary arterial hypertension. The following disease progression events were not significantly different among the two treatment groups: arrhythmia, pericardial effusion, renal crisis, and myositis. Comparisons in mortality rates are presented in Table 6.

Table 5. Characteristics of RCTs of HCT for Systemic Sclerosis

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Burt (2011) ASSIST	United States	1	2006 to 2009	Adult patients < 60 yrs with diffuse SSc; mRSS ≥ 15; internal organ involvement	High-dose intravenous cyclophosphamide 200 mg/kg; intravenous rabbit antithymocyteglobulin 6.5 mg/kg total dose; aHCT (n=10)	6 monthly treatments with intravenous pulsed cyclophosphamide (1000 mg/m^2) (n=9)
Van Laar (2014) ASTIS	9 European countries and Canada	29	2001 to 2009	Adult patients with diffuse cutaneous SSc; maximum duration 4 years; minimum mRSS >15; internal organ involvement	High-dose intravenous cyclophosphamide 200 mg/kg; intravenous rabbit antithymocyteglobulin 7.5 mg/kg total dose; aHCT (n=79)	12-monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m2) (n=77)
Sullivan (2018) SCOT	United States and Canada	26	2005 to 2011	Adult patients with scleroderma; maximum duration 5 years; active interstitial lung disease and scleroderma-related renal disease	Total body irradiation (800 cGy); cyclophosphamide (120 mg/kg); equine Antithymocyte globulin (90 mg/kg); aHCT (n=36)	12-monthly treatments with intravenous pulsed cyclophosphamide (n=39)

aHCT: autologous hematopoietic cell transplantation; HCT: hematopoietic cell transplantation; mRSS: modified Rodnan skin scores; RCT: randomized controlled trial

Table 6. Results of RCTs of HCT for Systemic Sclerosis

Study	Efficacy Outcomes		Adverse Events	TRM n (%)
Burt (2011) ASSIST	**mRSS at 1 year mean (SD)**	**FVC at 1 year Mean % (SD)**		
aHCT	15 (7.9)	74 (15.7)	NR	0
cyclophosphamide	22 (14.2)	61 (19.8)	NR	0

van Laar (2014) ASTIS	Events 1 year	Events 4 years	Deaths 1 year	Deaths 4 years	≥ Grade 3	TRM n (%)
aHCT	13	15	11	12	63%	8 (10.1)

cyclophosphamide	8	20	7	20	37%	0
Relative Risk (95% CI)	1.6 (0.7 to 4.4)	0.7 (0.4 to 1.3)	1.5 (0.4 to 5.4)	0.6 (0.3 to 1.1)		
Sullivan (2018)	**Global Rank Composite Score, at 4 years**		**Global Rank Composite Score, at 4,5 years**		**≥ Grade 3 Rate/person-yr**	**TRM N(%)**
aHCT	68%		67%		2.0	2 (5.5)
cyclophosphamide	32%		33%		1.2	0
p-value	0.008		0.01		<0.001	
	Death or Respiratory, Renal, or Cardiac Failure, n (%)		**Death from any cause, N (%)**			
aHCT	At 4 years: 10 (28)		At 4.5 years: 6 (17)			
cyclophosphamide	At 4 years: 20 (51)		At 4.5 years: 11 (28)			
p-value	0.06		0.28			

aHCT: autologous hematopoietic cell transplantation; CI: confidence interval; FVC: forced vital capacity; HCT: hematopoietic cell transplantation; mRSS: modified Rodnan skin scores; NR: not reported; RCT: randomized controlled trial; TRM: treatment-related mortality.

Nonrandomized Studies

Vonk et al (2008) reported the long-term results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HCT from 1998 to 2004.(31) There was 1 transplant-related death and 1 death due to progressive disease, leaving 26 patients for evaluation. After a median follow-up of 5.3 years (range, 1–7.5), 81% (n=21/26) of the patients demonstrated a clinically beneficial response. Skin sclerosis was measured with a modified Rodnan skin score, and a significant (i.e., >25%) decrease (i.e., improvement) was achieved in 19 of 26 patients after 1 year and 15 of 16 after 5 years. At study baseline, 65% of patients had significant lung involvement; all pulmonary function parameters remained stable after transplant at 5 and 7-year follow-ups. Based on the World Health Organization (WHO) performance status, which reflects the effect of HCT on the combination of functional status, skin, lung, heart and kidney involvement, the percentage of patients with a performance score of zero increased to 56% from 4% at baseline. Estimated survival at five years was 96.2% (95% confidence interval [CI]: 89–100%) and at 7 years was 84.8% (95% CI: 70.2–100%) and event-free survival, (survival without mortality, relapse or progression of systemic sclerosis resulting in major organ dysfunction) was 64.3% (95% CI: 47.9–86%) at 5 years and 57.1% (95% CI: 39.3–83%) at 7 years. For comparison, an international meta-analysis published in 2005 estimated the 5-year mortality rate in patients with severe systemic sclerosis at 40%.(32)

Nash et al (2007) reported the long-term follow-up of 34 patients with diffuse cutaneous systemic sclerosis with significant visceral organ involvement who were enrolled in a multi-institutional pilot study between 1997 and 2005 and underwent autologous HCT.(33) Of the 34 patients, 27 (79%) survived 1 year and were evaluable for response (there were 8 transplant-related deaths and 4 systemic sclerosis-related deaths). Of the 27 evaluable patients, 17 (63%) had sustained responses at a median follow-up of 4 years (range, 1 to 8 years). Skin biopsies showed a statistically significant decrease in dermal fibrosis compared with baseline ($p < 0.001$) and, in general, lung, heart, and kidney function remained stable. Overall function as assessed in 25 patients using the Disability Index of the modified Health Assessment Questionnaire showed improvement in 19, and disease response was observed in the skin of 23 of 25 and lungs of 8 of 27 patients. Estimated overall and progression-free survival were both 64% at 5 years.

Henes et al (2012) reported on 26 consecutive patients with systemic sclerosis scheduled for autologous HCT between 1997 and 2009.(34) The main outcome variable was response to treatment (reduction of modified Rodnan skin score [mRSS] by 25%) at 6 months. Secondary endpoints were transplant-related mortality (TRM) and PFS. At 6 months, significant skin and lung function improvement assessed on the mRSS was achieved in 78.3% of patients. Overall response rate was 91%, and some patients even improved after month 6. Three patients died between mobilization and conditioning treatment, 2 were due to severe disease progression and 1 treatment-related. Seven patients relapsed during the 4.4 years of follow up. PFS was 74%. Four patients died during follow-up, with the most frequent causes of death being pulmonary and cardiac complications of systemic sclerosis.

Henes et al (2020) described results from a prospective non-interventional study of 80 patients with systemic sclerosis between 2012and 2016.(35) After a median follow-up of 24 months after HCT, the primary endpoint of progression-free survival was 81.8%, and secondary endpoints of overall survival, response, and incidence of progression were 90%, 88.7%, and 11.9%, respectively. The incidence of non-relapse mortality at 100 days was 6.25%, and 4 patients experienced death from cardiac events, including 3 due to toxicity of cyclophosphamide used in conditioning regimens.

van Bijnen et al (2020) performed a retrospective cohort study of 92 patients in the Netherlands with systemic sclerosis treated with HCT between 1998 and 2017.(36) After a median follow up of 4.6 years, EFS at 5, 10, and 15 years were 78%, 76%, and 66%,respectively. From baseline to 5 years of follow up, median values decreased for modified RSS from 26 to 6 and increased for FVC from 84% to 94%. Disease progression occurred in 22 (24%) patients. Twenty patients died, and 10 deaths were classified as TRM.

Section Summary: Systemic Sclerosis (Scleroderma)
Evidence for the use of HCT in patients with systemic sclerosis/scleroderma consists of systematic reviews, 3 RCTs and several nonrandomized studies. All 3 RCTs report long term improvements in clinical outcomes such as modified RSS and FVC, as well as overall mortality in patients receiving autologous HCT compared with patients receiving chemotherapy alone. However due to small sample sizes in 2 of the RCTs, only the large RCT shows statistical significance. Treatment-related mortality and adverse events are higher among the patients receiving HCT compared with patients receiving chemotherapy alone.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systematic Review
Leone et al (2018) conducted a systematic review of clinical and laboratory studies using autologous HCT for patients with systemic lupus erythematosus (SLE).(37) The literature search, conducted through 2014, identified 25 studies (N=279 patients): 2 prospective, 10 retrospective, and 13 case reports. Quality assessment of included studies was not discussed in the publication. Heterogeneity between studies was high (I2=87%). The only pooled analysis conducted was on 5 studies reporting deaths, resulting in an overall mortality of 8.3% in a mean follow-up of 36 months.

Select case series from the systematic review by Leone et al (2018) and series published after the review are described below.

Burt et al (2006) published results from the largest single-center series using HCT for SLE in the United States.(38) Between 1997 and 2005, investigators enrolled 50 patients (mean age, 30 years, 43 women, 7 men) with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement in a single-arm trial. All subjects had at least 4 of 11 American College of Rheumatology criteria for SLE and required more than 20 mg/d of prednisone or its equivalent despite use of cyclophosphamide. Patients underwent autologous HCT following a lymphoablative-conditioning regimen. Two patients died after mobilization, yielding a treatment-related mortality rate of 4% (2/50). After a mean follow-up of 29 months (range, 6 months to 7.5 years), the 5-year overall survival rate was 84%, and the probability of disease-free survival was 50%. Several parameters of SLE activity improved, including renal function, SLE disease activity index (DAI) score, antinuclear antibody, anti-ds DNA, complement C3- and C4 levels, and carbon monoxide diffusion lung capacity. The investigators suggest these results justify a randomized trial comparing immunosuppression plus autologous HCT with continued standard of care.

Song et al (2011) reported on the efficacy and toxicity of autologous hematopoietic cell transplantation for 17 patients with SLE after 7 years follow-up.(39) OS and PFS rates were used to assess the efficacy and toxicities levels of the treatment. The median follow-up was 89 months (range 33-110 months). The probabilities of 7-year OS and PFS were 82.4% (SD=9.2% and 64.7% (SD=11.6%), respectively. The principal adverse events included allergy, infection, elevation of liver enzymes, bone pain, and heart failure. Two patients died, 1 due to severe pneumonia and the other due to heart failure at 33 and 64 months after transplantation, respectively. The authors concluded that their 7-year follow-up results suggested that autologous HCT was beneficial for SLE patients.

Leng et al (2017) reported on 24 patients with severe SLE who received high-dose immunosuppressive therapy and HCT.(40) Patients were followed for 10 years. One patient died following treatment. At the 6-month follow-up, 2 patients had achieved partial remission, and 21 patients had achieved remission. At the 10-year follow-up, the OS rate was 86%; 16 patients remained in remission, 4 were lost to follow-up, 2 patients had died, and 1 patient had active disease.

Cao et al (2017) reported on 22 patients with SLE who underwent autologous peripheral blood HCT.(41) At 5-year follow-up, PFS was 68% and overall survival was 95%. At last follow-up, 10 patients had relapsed. Adverse events included infections, secondary autoimmunity, lymphoma, and malignancy. The authors noted a difficulty in distinguishing between conditions caused by relapse or by the transplantation.

Burt et al (2018) reported on 30 patients with refractory, chronic, corticosteroid dependent SLE who underwent autologous HCT.(42) Outcomes were measured at 6 months and yearly through 5 years. Disease remission was achieved by 24 patients. The SLE Disease Activity Index and quality of life (SF- 36) improved significantly at each follow-up compared with baseline. No treatment-related mortality was reported. Five grade 4 and 60 grade 3 adverse events were reported.

Section Summary: Systemic Lupus Erythematosus
Evidence for the use of autologous HCT to treat patients with SLE consists of a systematic review and numerous case series. The systematic review did not conduct a quality

assessment and reported high heterogeneity among the studies. A 4% treatment-related mortality rate was reported in 2 studies. High rates of remission were reported at various follow-up times and adverse event rates were high. While HCT has shown beneficial effects on patients with SLE, further investigation of more patients is needed.

JUVENILE IDIOPATHIC OR RHEUMATOID ARTHRITIS

A review article by Saccardi et al (2008) on HCT for autoimmune diseases has summarized the experience with juvenile idiopathic and rheumatoid arthritis as follows.(43) More than 50 patients with juvenile idiopathic arthritis have been reported to the European Society for Blood and Marrow Transplantation (EBMT) Registry. The largest cohort study initially used a single conditioning regimen, and thereafter, a modified protocol. Overall drug-free remission rate was approximately 50%. Some late relapses have been reported, and only partial correction of growth impairment has been seen. The frequency of HCT for rheumatoid arthritis has decreased significantly since 2000, due to the introduction of new biologic therapies. Most patients who have undergone HCT have had persistence or relapse of disease activity within 6 months of transplant.

Case Series

Silva et al (2018) reported on 16 patients with JIA refractory to standard therapy or who had failed autologous HCT, who underwent allogeneic HCT.(44) Patients experienced significant improvements in arthritis and quality of life, with 11 children achieving drug-free remission at last follow-up. At median follow-up of 29 months, one patient died of probable sepsis following an elective surgery and one died of invasive fungal infection, for a treatment-related mortality rate of 12.5%.

Section Summary: Juvenile Idiopathic or Rheumatoid Arthritis

Evidence for the use of HCT on patients with juvenile idiopathic arthritis consists of data from an EBMT Registry (N>50). Different conditioning regimens were used among the patients in the registry, with remission rates averaging 50%. However, relapse has been reported within 6 months in many cases, and new biologic therapies that provide improved outcomes are available for these patients. The case series of patients with refractory JIA reported a high rate of drug-free remission (69%),with a treatment-related mortality rate of 12.5%.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Systematic Review

Several review articles have summarized experience with HCT in treatment of chronic inflammatory demyelinating polyneuropathy.(45-47) In general, the evidence includes a few case reports describing outcomes of autologous HCT in patients who failed standard treatments such as corticosteroids, intravenous immunoglobulins, and plasma exchange. While improvements were reported, some with long-term follow-up, the numbers of patients undergoing the procedure are small, and the potential for serious adverse events is a concern.

Nonrandomized Studies

Burt et al (2020) reported results from a single-center, open-label prospective cohort of 60 patients with chronic inflammatory demyelinating polyneuropathy treated with HCT (Table 7).(48) Patients were required to have failed 2 of 3 first-line treatments(corticosteroids, intravenous immune globulin, or plasmapheresis). Results for key endpoints are reported in Table 8. No treatment-related mortality occurred, and 3 (4.5%) patients experienced grade 4

toxicities (hypokalemia, use of continuous positive airway pressure for dyspnea, and use of total parenteral nutrition for nausea and vomiting).

Table 7. Characteristics of Observational Studies of HCT for Chronic Inflammatory Demyelinating Polyneuropathy

Study	Study Design	Country	Participants	N	Follow-Up, median years (range)
Burt (2020)	Prospective cohort	United States	Patients with CIDP who failed at least 2 of 3 first-line treatments	60	4.5 (2 to 5)

CIDP: chronic inflammatory demyelinating polyneuropathy.

Table 8. Results of Observational Studies of HCT for Chronic Inflammatory Demyelinating Polyneuropathy

Study	OS, % (95% CI)	Medication-free remission (%)	Ambulation-free assistance (%)
Burt (2020)	97 (NR)	1 year: 80 2 years: 78 3 years: 76 4 years: 78 5 years: 83	1 year: 82 2 years: 82 3 years: 81 4 years: 86 5 years: 83

CI: confidence interval; NR: not reported; OS: overall survival.

Section Summary: Chronic Inflammatory Demyelinating Polyneuropathy

Evidence for the use of HCT to treat patients with chronic inflammatory demyelinating polyneuropathy is limited to a recent observational study and case reports. Additional investigations are needed due to the toxicity associated with this procedure.

TYPE 1 DIABETES MELLITUS

Systematic Reviews

Sun et al (2020) published a meta-analysis on the use of HCT to treat type 1 diabetes using data from RCTs published to March 2019(Tables 9 and 10).(49) The authors included randomized and non-randomized studies in the systematic review but performed a quantitative meta-analysis using only data from randomized studies; these results are presented in Tables 10 and 11. Most domains of bias in the RCTs were rated as low or unclear risk. Results of the meta-analysis found that, compared with insulin therapy, HCT therapy significantly reduced HbA1c levels, increased fasting C-peptide levels (C-peptide measures islet cell mass, and an increase after HCT indicates preservation of islet cells), and reduced insulin dosages at 6 months of treatment, while not significantly increasing risk of adverse events. The authors concluded HCT for type 1 diabetes may improve glycemic control and beta cell function without increasing risk of adverse events.

El-Badawy and El-Badri (2016) published a meta-analysis on the use of HCT to treat diabetes (Tables 9 and 10).(50) The literature search, conducted through August 2015, identified 22 studies for inclusion; study designs were not consistently reported. Fifteen of the studies (n=300 patients) involved patients with type I diabetes; seven studies (n=224 patients) involved patients with type 2 diabetes. Results for the cohort of patients with type 1 diabetes are presented in Table 11. The quality of the selected studies was assessed using Cochrane criteria; however, results of the risk of bias assessment were not reported in the publication. The mean follow-up in the studies ranged from 6 to 48 months (median, 12 months). Table 12 presents comparisons of C-peptide levels and hemoglobin A1c levels after 12-month follow-up. Adverse events were reported in 22% of the patients, with no reported mortality. Reviewers

concluded that remission of diabetes is possible and safe with stem-cell therapy, patients with previously diagnosed ketoacidosis are not good candidates for HCT, and that early-stage patients may benefit more from HCT. Large-scale well-designed randomized studies considering stem-cell type, cell number, and infusion method is needed.

Table 9. Comparison of Studies Included in Systematic Reviews of Studies of Patients with Diabetes Treated with HCT

Study	Sun (2020)	El-Badawy and El-Badri (2011)
Cai (2016)	●	
Carlsson (2015)	●	●
Ghodsi (2012)	●	
Hu (2013)	●	●
Zhang (2016)	●	●
Gu (2018)	●	●
Gu (2014)	●	●
Hou (2014)	●	●
Walicka (2018)	●	●
Wang (2013)	●	●
Ye (2017)	●	●
Yu (2011)	●	●
Zhao (2012)	●	●
Thakkar (2015)		●
D'Addio (2014)		●
Haller (2013)		●
Bhansali (2013)		●
Giannopoulou (2013)		●
Mesples (2013)		●
Li (2012)		●
Zhang (2012)		●
Gu (2012)		●
Haller (2011)		●
Snarski (2010)		●
Vanikar (2010)		●
Couri (2009)		●
Haller (2009)		●
Liu (2014)		●
Wu (2014)		●
Tong (2013)		●
Hu (2012)		●
Jiang (2011)		●
Bhansali (2009)		●

HCT: hematopoietic cell transplantation

Table 10. Summary of Systematic Reviews of Studies of Patients with Diabetes Treated with HCT

Study	Dates	Studies	Participants	N (range)	Duration
Sun (2020)	To March 2019	13 (5 RCTs, 8 non-randomized studies)	Patients with type 1 diabetes	396 (3 to 28) (RCTs and non-randomized studies) 154 (20 to 42) (RCTs only)	12 to 50 months
El-Badawy and El-Badri (2011)[45,]	To August 2015	22	Patients with type 1 diabetes (15 studies;	524 (8 to 118)	6 to 48 months

		n=300); patients with type 2 diabetes (7 studies; n=224)

RCT: randomized controlled trial.

Table 11. Results of Systematic Reviews of Studies of Patients with Diabetes Treated with HCT

Study	Efficacy Outcomes			Adverse Event	
	C-peptide levels	*HbA1c*	*Insulin dosage*	*Infection*	*Gastrointestinal symptoms*
Sun (2020)					
Total N	151	71	93	88	88
Pooled effect (95% CI)	MD, -1.20 (-1.91 to -0.49)	MD, -1.20 (-1.91 to -0.49)	SMD, -3.35 (-7.02 to 0.32)	RR, 0.97 (0.40 to 2.34)	RR, 0.69 (0.14 to 3.28)
I^2 (p)	96% (0.00001)	96% (0.00001)	96% (<0.00001)	45% (0.95)	0% (0.64)
Range of N	18 to 42	18 to 42	18 to 42	NR	NR
Range of effect sizes	-0.10 to -2.07	-0.10 to -2.07	0 to -6.38	NR	NR
El-Badawy and El-Badri (2011)					
Total N	199	193	NR	NR	NR
Pooled effect (95% CI)	SMD vs baseline, -0.57 (-0.79 to -0.35)	SMD vs baseline, 1.09 (0.83 to 1.35)			
I^2 (p)	90% (<0.00001)	96% (<0.00001)			
Range of N	7 to 65	7 to 65			
Range of effect sizes	-1.37 to 1.07	0.05 to 3.87			

CI: confidence interval; HbA1c: hemoglobin A1c; HCT: hematopoietic cell transplantation; MD: mean difference; NR: not reported; RR: relative risk; SMD: standardized mean difference.

Table 12. Standard Mean Differences From Baseline in C-Peptide and HbA_{1c} Levels in Patients with Diabetes Treated with HCT after 12 Months of Follow-up

Diabetes Subgroups	No. of Studies	No. of Patients	SMD (95% CI) C-Peptide	No. of Studies	No. of Patients	SMD (95% CI) HbA_{1c}
Type 1						
UCB	4	56	1.07 (0.67 to 1.48)	4	61	0.95 (-0.30 to 0.41)
UC-MSC	1	15	-0.91 (-1.67 to -0.16)	1	15	1.19 (0.41 to 1.98)
BM-HSC	4	97	-1.37 (-1.69 to -1.05)	3	96	3.87 (3.29 to 4.44)
BM-MSC	1	10	-1.18 (-2.15 to -0.22)	NA	NA	NA
IS-ADSc + BM-HSC	2	21	-1.01 (-1.73 to -0.30)	2	21	0.93 (0,27 to 1.59)
Total	12	199	-0.57 (-1.73 to -0.35)	10	193	1.09 (0.83 to 1.35)

Adapted from El-Badawy and El-Badri (2016).
BM-HSC: bone marrow hematopoietic stem cells; BM-MSC: bone marrow mesenchymal stem cells; CI: confidence interval; HbA_{1c}: hemoglobin A_{1c}; HCT: hematopoietic cell transplantation; IS-ADSc: insulin secreting-adipose derived stem cells; NA: not applicable; SMD: standard mean difference; UCB: umbilical cord blood; UC-MSC: umbilical cord mesenchymal stem cells.

Case Series

Several case series evaluated autologous HCT in patients with new-onset type 1 diabetes; there were no published comparative studies. Although a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high.

Cantu-Rodriguez et al (2016) published a study of 16 patients with type 1 diabetes who received a less toxic conditioning regimen and transplantation.(51) The outpatient procedures were completed without severe complications. At the 6-month follow-up, 3 (19%) were non-responders, 6 (37%) partially independent from insulin, and 7 (44%) were completely independent of insulin. Hemoglobin A1c levels decreased by a mean of -2.3% in the insulin-independent group.

Xiang et al (2015) published data on 128 patients ages 12 to 35 years who had been diagnosed with type 1 diabetes no more than 6 weeks before study enrollment.(52) After a mean follow-up of 28.5 months (range, 15-38 months), 71 (55%) patients were considered to be insulin-free. These patients had a mean remission period of 14.2 months. The other 57 (45%) patients were insulin-dependent. The latter group included 27 patients with no response to treatment and another 30 patients who relapsed after a transient remission period. Adverse events included ketoacidosis and renal dysfunction (1 patient each); there was no transplant-related mortality. In multiple logistic regression analysis, factors independently associated with becoming insulin-free after autologous HCT were younger age at onset of diabetes, lower tumor necrosis factor α levels, and higher fasting C peptide levels.

A case series by Snarski et al (2016) reported on 24 patients with a diagnosis of type I diabetes who underwent autologous HCT.(8) Mean age was 26.5 years (range, 18-34 years). After treatment, 20 (87%) of 23 patients went into diabetes remission, defined as being insulin-free with normoglycemia for at least 9.5 months. The median time of remission was 31 months (range, 9.5-80 months). Mean insulin doses remained significantly lower than baseline doses at 2 and 3 years, but the insulin doses returned to pre-HCT levels at years 4 and 5. Among 20 patients remaining in follow-up at the time of data analysis for publication, 4 (20%) remained insulin-free. In an update published by Walicka et al (2018), after 6 years of follow-up, 1 patient remained insulin-free.(53) Adverse events include neutropenic fever in 12 patients (50%). There were 4 cases of sepsis, including a fatal case of *Pseudomonas aeruginosa* sepsis. There was also a case of pulmonary emphysema after insertion of a central venous catheter.

Section Summary: Type 1 Diabetes
Evidence for the use of HCT to treat diabetes consists of several case series and 2 meta-analysis. The meta-analyses revealed that HCT may improve HbA1, and C-peptide levels compared with baseline values and compared with insulin. One meta-analysis found that HCT is more effective in patients with type I diabetes, compared with type 2 diabetes, and when the treatment is administered soon after the diagnosis. Certain factors limit the conclusions that can be drawn about the overall effectiveness of HCT to treat diabetes; due to heterogeneity in the stem-cell types, cell number infused, and infusion methods. Case series reported short term effectiveness in achieving insulin independence; however, long term studies showed that a majority of patients returned to insulin within 4 to 6 years.

OTHER AUTOIMMUNE DISEASES

Review of Evidence

Crohn Disease
Phase 2/3 protocols are being developed for Crohn disease.

Hawkey et al (2015) has conducted the only RCT (ASTIC trial; NCT00297193) evaluating the effect of HCT on Crohn disease.(54) Patients were randomized to receive either immunoablation and HCT (n=23) or control (HCT deferred for 1 year, n=22). The primary endpoint was remission defined as: Crohn Disease Activity Index <150; no use of corticosteroids or immunosuppressive drugs or biologics for 3 months; and no endoscopic or radiologic evidence of active disease. At 1-year follow-up, 2 patients in the treatment group and 1 patient in the control group achieved remission (p=0.6). Adverse events were reported in 76 patients receiving HCT and in 38 controls. One HCT patient died.

Lindsay et al (2017) reported additional analyses on the ASTIC trial participants, combining the treatment patients and the control patients who underwent deferred HCT.(55) Outcomes were three-month steroid-free clinical remission at one year and degree of endoscopic healing at one year. Three-month steroid free clinical remission was achieved by 13 of 34 (38%; 95% CI, 22% to 55%) patients who had data available. Complete endoscopic healing was seen in 19 of 38 patients (50%; 95% CI, 34% to 66%). However, serious adverse events (76) were experienced in 23 of 40 patients.

Brierley et al (2018) published a review of patients in the European Society for Blood and Marrow Transplantation registry undergoing autologous HCT for Crohn disease (n=82) who had failed a median of 6 lines of drug therapy.(56) At median follow-up of 41 months, 68% achieved either complete remission or significant improvement in symptoms. One patient died of causes relating to the transplant (cytomegalovirus infection, sepsis, and organ failure). At a median of 10 months follow-up, 73% resumed medical therapy for Crohn disease.

Additional Autoimmune Diseases
For the remaining autoimmune diseases (including immune cytopenias, relapsing polychondritis), sample sizes are too small to draw conclusions.

A case series of 7 patients with myasthenia gravis was reported by Bryant et al (2016).(57) Using the Myasthenia Gravis Foundation of America clinical classification, all patients achieved complete stable remission, with follow-up from 29 to 149 months. The authors concluded that these positive long-term results warranted further investigation of HCT for patients with myasthenia gravis.

Section Summary: Other Autoimmune Diseases
Evidence for the use of HCT to treat Crohn disease consists of an RCT and a retrospective review of registry data. While remission was experienced by some patients receiving HCT, adverse event rates were high, and many patients had recurrence of symptoms within 1 year.

Evidence for the use of HCT for other autoimmune diseases consists of case series. Information from larger prospective studies is needed.

SUMMARY OF EVIDENCE
For individuals with relapsing-remitting multiple sclerosis who receive hematopoietic cell transplantation (HCT), the evidence includes 2 RCTs, systematic reviews, several nonrandomized studies, and consensus guidelines. The relevant outcomes are overall survival, health status measures, quality of life, and treatment-related mortality (TRM) and morbidity. Although large clinical trials and observational studies are not available regarding the efficacy of autologous HCT in multiple sclerosis, HCT/immune effector cell therapy (IECT)

has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multi-center cohort studies. One RCT compared HCT with mitroxantrone and the trial reported intermediate outcomes (number of new T2 magnetic resonance imaging lesions); the group randomized to HCT developed significantly fewer lesions than the group receiving conventional therapy. The findings of the nonrandomized studies revealed improvements in clinical parameters following HCT compared with baseline. Outcomes in the single-arm studies included PFS, relapse-free survival, disease activity-free survival, disability worsening-free survival, disease stabilization, number of new lesions, and improvements in EDSS scores. Improvements were seen in all outcomes compared with baseline. HCT/IECT can be considered as a treatment option for individuals after careful evaluation of risks and benefits. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes 3 RCTs and observational studies. The relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality, and morbidity. All 3 RCTs compared cyclophosphamide conditioning plus autologous HCT with cyclophosphamide alone. Patients in the RCTs were adults <60 years of age, maximum duration of disease of 5 years, with modified Rodnan skin scores (RSS) >15, and internal organ involvement. Short term results of the RCTs show higher rates of adverse events and treatment-related mortality among patients receiving autologous HCT compared with patients receiving chemotherapy alone. However, long term improvements (four years) in clinical outcomes such as modified RSS and forced vital capacity, as well as overall mortality in patients receiving HCT compared with patients receiving cyclophosphamide alone were consistently reported in all RCTs. Due to sample size limitations in 2 of the RCTs, statistical significance was found only in the larger RCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcomes.

For individuals with systemic lupus erythematosus who receive HCT, the evidence includes a systematic review and case series. Relevant outcomes are overall survival, symptoms, quality of life and treatment-related mortality and morbidity. Studies were heterogeneous in conditioning regimens and source of cells. The largest series (N=50) reported on an overall 5-year survival rate of 84% and the probability of disease-free survival was 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with juvenile idiopathic or rheumatoid arthritis who receive HCT, the evidence includes registry data and a case series. Relevant outcomes are overall survival, symptoms, quality of life, and treatment-related mortality and morbidity. The registry included 50 patients with juvenile idiopathic or rheumatoid arthritis. The overall drug-free remission rate was approximately 50% in the registry patients and 69% in the smaller case series. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with chronic inflammatory demyelinating polyneuropathy who receive HCT, the evidence includes 1 observational study and case reports. The relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with type I diabetes mellitus who receive HCT, the evidence includes case series and 2 meta-analyses. The relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. While a substantial proportion of patients tended to become insulin free after HCT, remission rates were still high. The meta-analyses further revealed that HCT is more effective in patients with type I diabetes, compared with type 2 diabetes, and when HCT is administered soon after the diagnosis. Certain factors limit the conclusions that can be drawn about the overall effectiveness of HCT in treating diabetes; those factors are: heterogeneity in the stem cell types, cell number infused, and infusion methods. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes 1 RCT, small retrospective studies and case series. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. The RCT was conducted on patients with Crohn's disease. At one-year follow-up, one patient in the control group and two patients in the HCT group achieved remission. Data are needed from additional controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Neurology(AAN): Endorsed by the Consortium of multiple Sclerosis Centers the Multiple Sclerosis Association of America, and the National Multiple Sclerosis Society.
Per the recommendation of the AAN (2018) the following recommendations were made:

- Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with MS with highly active MS. (Level B)
- Ocrelizumab is the only DMT shown to alter disease progression in individuals with primary progressive multiple sclerosis (PPMS) who are ambulatory, therefore clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (level B)
- Clinicians should discuss switching from 1 DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
    - Ongoing disease activity, measured either by clinical relapses or new MRI-detected lesions (including unequivocally new T2 or new gadolinium-enhanced lesion(s).
    - Many clinicians obtain new baseline MRI 3 to 6 months after initiating DMTs

American Society for Transplantation and Cellular Therapy
The American Society for Transplantation and Cellular Therapy (2020) published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial

setting.(58) Table 13 summarizes recommendations for specific indications addressed in this guideline.

Table 13. Recommendations for the Use of HCT to Treat Autoimmune Diseases

Indications for HCT in Pediatric Patients (Generally < 18 y)	Allogeneic HCT[a]	Autologous HCT[a]
Juvenile rheumatoid arthritis	D	R
Systemic sclerosis	D	R
Other autoimmune and immune dysregulation disorders	R	N
Indications for HCT in Adults > 18 y		
Multiple sclerosis	N	C
Systemic sclerosis	N	S
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn disease	N	D
Polymyositis-dermatomyositis	N	D

HCT hematopoietic cell transplantation; [a]"Standard of care (S): This category includes indications that are well defined and are generally supported by evidence in the form of high-quality clinical trials and/or observational studies (e.g., through CIBMTR or EBMT)." "Standard of care, clinical evidence available I: This category includes indications for which large clinical trials and observational studies are not available. However, HCT/immune effector cell therapy (IECT) has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multi-center cohort studies. HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits. As more evidence becomes available, some indications may be reclassified as 'Standard of Care'"" "Standard of care, rare indications(R): Indications included in this category are rare diseases for which clinical trials and observational studies with sufficient number of patients are not currently feasible because of their very low incidence. How-ever, single-center or multicenter or registry studies in relatively small cohorts of patients have shown HCT/IECT to be effective treatment with acceptable risks of morbidity and mortality. For patients with diseases in this category, HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits." "Developmental; (D): Developmental indications include diseases where pre-clinical and/or early phase clinical studies show HCT/IECT to be a promising treatment option. HCT/IECT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as 'Standard of Care, Clinical Evidence Available' or 'Standard of Care'." "Not generally recommended (N): HCT/IECT is not currently recommended for these indications where evidence and clinical practice do not support the routine use of HCT/IECT. However, this recommendation does not preclude investigation of HCT/IECT as a potential treatment and may be pursued for these indications within the context of a clinical trial

American Society for Blood and Marrow Transplantation (ASBMT)

The ASBMT (2019) released guidelines which endorse *autologous* hematopoietic cell transplantation as a standard of care for treatment-refractory relapsing multiple sclerosis in individuals with relapsing forms of multiple sclerosis (or progressive multiple sclerosis with superimposed activity) who have prognostic factors that indicate a high risk of future disability, including ongoing clinical relapse or MRI lesion activity despite treatment with available disease-modifying therapies, especially if disease activity continues despite treatment with high-efficacy disease-modifying therapies and/or worsening disability.(61)

The German Multiple Sclerosis Competence Network Taskforce for Autologous Haematopoietic Stem Cell Transplantation

The German Multiple Sclerosis Competence Network Taskforce for AHSCT (2023) provided a consensus-based opinion paper authored by 25 experts on the up-to-date optimal use of AHSCT in managing MS based on the Swiss criteria. Current data indicates that individuals who are most likely to benefit from AHSCT, have relapsing-remitting MS, are young, ambulatory and have high disease activity (i.e., relapses or new magnetic resonance imaging (MRI) lesions). For advanced disease stages with a long duration, older age and greater impairment, data argue against a benefit that would justify the risks of transplantation. Recommendations are as follows:

Table 14. Recommendations per the German MS Competence Network for AHSCT

Parameter	Core criteria	Extended criteria

Age (years)	18–45	46–55
EDSS	3.0–6.0[a]	≤ 6.5
Duration of illness (years)	≤ 10	≤ 15
Disease course	• RRMS or • SPMS with progression for ≤ 2 years	• RRMS or • SPMS with progression for ≤ 5 years
Clinical activity in the last 12–24 months	Within 12 months before: • ≥ 1 relapse with EDSS increase[b] or • ≥ 2 relapses with or without EDSS increase[b]	Within 24 months before: • ≥ 1 relapse with or • without EDSS increase[b]
Clinical progression in the last 12–24 months	Within 12 months before: Increase in EDSS[b]	Within 24 months before: • Increase in EDSS[b] or • increase in other scores (MSFC) by ≥ 20%.
MRI activity in the last 12–24 months[b]	Within 12 months before: • ≥ 1 Gd+ Lesion or • ≥ 1 new or enlarged T2 hyperintense lesions ≥ 3 mm	In the last 24 months: • ≥ 1 Gd+ Lesion or • ≥ 1 new or enlarged T2 hyperintense lesions ≥ 3 mm
Therapy failure	Failure of ≥ 1 highly active substance (ocrelizumab, ofatumumab, rituximab, natalizumab, alemtuzumab or similar active)	Failure of at least 1 MS therapy

EDSS, Expanded Disability Status Scale Score; MRI, magnetic resonance imaging; MSFC, Multiple Sclerosis Functional Composite; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.
[a]In the case of progression during relapse, higher EDSS values can be present that justify an AHSCT, just as values < 3.0 can be present in a relapse-free interval.
[b]Increase in EDSS: 1 point for patients with EDSS < 5.5, 0.5 points for EDSS ≥ 5.5.

The German Multiple Sclerosis Competence Network Taskforce also indicated that:

- In individuals with clearly aggressive disease, AHSCT might be justified even as a first-line treatment on a case-by-case basis.
- AHSCT should be considered with great caution when used in individuals with primary progression multiple sclerosis (PPMS). Ideally, these patients fulfill activity criteria through MRI activity and imposed relapses. Without MRI activity, PPMS could only be considered in cases with an aggressive course that is, EDSS 6.0 after 5 years or EDSS 6.0 before age 40 and with enhanced consideration of the benefit versus risk balance.(62)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently ongoing and unpublished trials that might influence this review are listed in Table 14.

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02674217	Outpatient Hematopoietic Grafting in Patients with Multiple Sclerosis Employing Autologous Non-cryopreserved Peripheral Blood Stem Cells: a Feasibility Study	200	Dec 2025
NCT01895244	High-dose Chemotherapy and Transplantation of 43+ Selected Stem Cells for Progressive Systemic Sclerosis - Modification According to Manifestation	44	Sep 2022

NCT03477500	Randomized Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients with Relapsing Remitting Multiple Sclerosis	100	Mar 2024
NCT04047628	A Multicenter Randomized Controlled Trial of Best Available Therapy Versus Autologous Hematopoietic Stem Cell Transplant for Treatment-Resistant Relapsing Multiple Sclerosis (ITN077AI)	156	Oct 2029
NCT03219359	Maintenance in Autologous Stem Cell Transplant for Crohn's Disease (–ASCT - CD)	50	Oct 2030
NCT00716066	High-Dose Immunosuppressive Therapy Using Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) + Thymoglobulin Followed by Syngeneic or Autologous Hematopoietic Cell Transplantation for Patients with Autoimmune Neurologic Diseases	80	Jun 2033
NCT05029336	Autologous Stem Cell Transplant (ASCT) for Autoimmune Diseases	20	May 2031
NCT03000296	Autologous Unselected Hematopoietic Stem Cell Transplantation for Refractory Crohn's Disease	50	Dec 2024
NCT04464434	Upfront Autologous Hematopoietic Stem Cell Transplantation Versus Immunosuppressive Medication in Early Diffuse Cutaneous Systemic Sclerosis: an International Multicentre, Open-label, Randomized Con-trolled Trial	50	Oct 2030
NCT04047628	Best Available Therapy Versus Autologous Hematopoetic Stem Cell Transplant for Multiple Sclerosis (BEAT-MS)	156	Jan 2024
Unpublished			
NCT03562208[a]	Autologous Bone Marrow Transplant in Chronic Insulin Dependent Diabetic Patients Phase II Clinical Trial	100	Jun 2020
NCT03069170	Safety and Efficacy of Immuno-Modulation and Autologous Bone-Marrow Derived Stem Cell Transplantation for the Treatment of Multiple Sclerosis	50	Jan 2021
NCT03113162	Evaluation of the Safety and Efficacy of Reduced-Intensity Immunoablation and Autologous Hematopoietic Stem Cell Transplantation (AHSCT) in Multiple Sclerosis	15	May 2022
NCT00750971	An Open-Label, Phase II Multicenter Cohort Study of Immunoablation with Cyclophosphamide and Antithymocyte-Globulin and Transplantation of Autologous CD34-Enriched Hematopoietic Stem Cells versus Currently Available Immunosuppressive /Immunomodulatory Therapy for Treatment of Refractory Systemic Lupus Erythematosus	30	Aug 2020

NCT: national clinical trial.
[a]Denotes industry sponsored or co-sponsored trial.

Government Regulations
National

There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services have not issued a national coverage determination (NCD) for stem cell transplantation for each disease. CMS has a general NCD for stem cell transplantation.

Medicare National Coverage Determinations Manual 100-03, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 1/27/16; Implementation Date: 10/3/16

General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion.

Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Indications and Limitations of Covee

A. Nationally Covered Indications

I. Allogeneic Hematopoietic STEM CELL Transplantation (HSCT)

a) Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
b) Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
c) Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

MDS refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood **CELL**s. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics. The abnormal production of blood **CELL**s in the bone marrow leads to low blood **CELL** counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow

Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study. (see Medicare guideline for more information)

II. Autologous STEM CELL transplantation (A)

C) a) Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §l862(a)(1)(A) of the Act for the following conditions and is covered under Medicare for patients with:

1. Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched;
2. Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
3. Recurrent or refractory neuroblastoma; or,
4. Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

b) Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
- Adequate cardiac, renal, pulmonary, and hepatic function.

c) Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

- Amyloid deposition in 2 or fewer organs; and,
- Cardiac left ventricular ejection fraction (EF) greater than 45%.

B. Nationally Non-Covered Indications

I. Allogeneic Hematopoietic STEM CELL transplantation (HSCT)

a) Effective for claims with dates of service on or after May 24, 1996, through January 26, 2016, allogeneic HSCT is not covered as treatment for multiple myeloma.

II. Autologous STEM CELL transplantation (A)

C) a) Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:

- Acute leukemia not in remission;
- Chronic granulocytic leukemia;
- Solid tumors (other than neuroblastoma);
- Up to October 1, 2000, multiple myeloma;
- Tandem **transplant**ation (multiple rounds of AuSCT) for patients with multiple myeloma;
- Effective October 1, 2000, non-primary AL amyloidosis; and,
- Effective October 1, 2000, through March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §l862(a)(1)(A) of the Act and is not covered under Medicare.

C. Other

All other indications for STEM CELL TRANSPLANTATION not otherwise noted above as covered or non-covered remain at local Medicare Administrative Contractor discretion.

(This NCD last reviewed January 2024.)

Local:

There is no local coverage determination on this topic. Refer to NCD.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Breast Cancer (Retired)
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias (Allogeneic)
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Malignant Astrocytomas and Gliomas (Autologous)
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through May 9, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/11	8/16/11	8/16/11	Joint policy established. *Note: This policy was generated from former combined policies on investigational bone marrow transplants*
3/1/14	12/10/13	1/6/14	Routine update. No change in policy status. CPT codes for transplants and applicable lab codes added to policy
9/1/15	6/19/15	7/16/15	Routine update. Added Medicare coverage information
9/1/16	6/21/16	6/21/16	Routine policy maintenance. Updated references and rationale sections. No change in policy status.
9/1/17	6/20/17	6/20/17	Routine maintenance Changed hematopoietic stem cell transplant (except for quoted Medicare information) to hematopoietic cell transplant (HCT) Updated National Coverage Determination
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/20	6/16/20		Systemic sclerosis was changed from investigational to established
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (slp) Vendor managed: N/A
9/1/24	6/13/24		• Routine maintenance (slp) • Vendor Managed: N/A • Policy updated to allow coverage for MS

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT-HEMATOPOIETIC CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered with criteria.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.