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Hematopoietic Cell Transplantation for Autoimmune Diseases

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Related Policies (if applicable)
SUR703.002: Hematopoietic Cell Transplantation (HCT) or Additional Infusion Following Preparative Regimens (General Donor and Recipient Information)

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Autologous hematopoietic cell transplantation (HCT) **may be considered medically necessary** as a treatment of systemic sclerosis (scleroderma) if all of the following conditions are met:

- Adult individuals <60 years of age; AND
- Maximum duration of condition of 5 years; AND
- Modified Rodnan Scale Scores ≥15; AND
- Internal organ involvement as noted in the Policy Guidelines; AND
- History of <6 months treatment with cyclophosphamide; AND
- No active gastric antral vascular ectasia; AND
- Do not have any exclusion criteria as noted in the Policy Guidelines.

Autologous HCT as a treatment of systemic sclerosis/scleroderma not meeting the above criteria **is considered experimental, investigational and/or unproven.**

Autologous or allogeneic HCT **is considered experimental, investigational and/or unproven** as a treatment of autoimmune diseases, including, but not limited to, the following:

- Multiple sclerosis (MS),
- Systemic lupus erythematosus (SLE),
- Juvenile idiopathic or rheumatoid arthritis (RA),
- Chronic inflammatory demyelinating polyneuropathy (CIDP), and
- Type 1 diabetes mellitus.

Policy Guidelines

Autologous hematopoietic cell transplantation (HCT) should be considered for individuals with systemic sclerosis only if the condition is rapidly progressing and the prognosis for survival is poor. An important factor influencing the occurrence of treatment-related adverse effects and response to treatment is the level of internal organ involvement. If organ involvement is severe and irreversible, HCT is not recommended. Below are clinical measurements that can be used to guide the determination of organ involvement.

Individuals with internal organ involvement indicated by the following measurements may be considered for autologous HCT:

- Cardiac: abnormal electrocardiogram; OR
- Pulmonary: diffusing capacity of carbon monoxide (DLCo) <80% of predicted value; decline of forced vital capacity (FVC) of ≥10% in last 12 months; pulmonary fibrosis; ground glass appearance on high-resolution chest computed tomography *(*CT); OR
- Renal: scleroderma-related renal disease.

Individuals with internal organ involvement indicated by the following measurements should not be considered for autologous HCT:

- Cardiac: left ventricular ejection fraction <50%; tricuspid annular plane systolic excursion <1.8 cm; pulmonary artery systolic pressure >40 mm Hg; mean pulmonary artery pressure >25 mm Hg.
- Pulmonary: DLCo <40% of predicted value; FVC <45% of predicted value.
- Renal: creatinine clearance <40 ml/minute.

Description

Most individuals with autoimmune disorders respond to conventional drug therapies; 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. It is in this group of individuals with a 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 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, immunosuppressants, 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 HCT. The primary concept underlying the use of HCT for these diseases is this: 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

Hematopoietic cell transplantation is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. The term HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without 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 the 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 existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host (GVHD) disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the

patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-Intensity Conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC 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 is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial GVM effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full donor chimerism. In this policy, the term *reduced-intensity conditioning* will refer to all conditioning regimens intended to be nonmyeloablative.

Regulatory Status

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

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be

adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

AUTOIMMUNE DISEASES

Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including multiple sclerosis (MS), systemic sclerosis/scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), 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 hematopoietic cell transplantation (HCT) in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablation) and generate new, self-tolerant lymphocytes. While evidence for the use of allogeneic HCT (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, patients 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 MS (n=379), systemic sclerosis (n=207), SLE (n=92), RA (n=88), juvenile idiopathic arthritis (JIA; n=70), idiopathic thrombocytopenic purpura (ITP; n=23), and Crohn disease (CD; n=23). (3)

Multiple Sclerosis

Clinical Context and Therapy Purpose

The purpose of HCT in individuals who have MS 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 policy.

Populations

The relevant population of interest is individuals with multiple sclerosis.

Interventions

The therapy being considered is HCT.

Comparators

Comparators consist of conventional medication 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 (OS), health status measures, QOL, treatment-related mortality (TRM), and treatment-related morbidity. Specific outcomes of interest include progression-free survival (PFS) 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 a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-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.

Systematic Reviews
Characteristics of systematic reviews are presented in Tables 1 and 2 and results of systematic reviews are presented in Table 3.

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. (4) Fourteen studies met inclusion criteria, of which 8 case series met inclusion criteria for the primary outcome of 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. The studies differed in the types and intensities of conditioning regimens used before HCT, with 5 studies using an intermediate-intensity regimen and 3 using high-intensity regimens. All studies were rated moderate quality. 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. The rates 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 PFS and disease activity-free survival, as well as 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, RRMS 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 after treatment (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 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. Comparison of Studies Included in MS SR & M-A

Study	Reston et al. (2011) (4)	Sormani et al. (2017) (5)	Ge et al. (2019) (6)	Nabizadeh et al. (2022) (7)
Abrahamsson et al. (2013)				●
Alping et al. (2020)				●
Arruda et al. (2014)				●
Atkins et al. (2016)		●	●	●
Blanco et al. (2004)				●
Boffa et al. (2021)				●
Bonechi et al. (2014)				●
Bose et al. (2019)				●
Bowen et al. (2012)		●	●	●

Burman et al. (2014)		●	●	
Burt et al. (2003)	●	●	●	
Burt et al. (2015)		●	●	
Burt et al. (2021)				●
Casanova et al. (2017)			●	●
Chen et al. (2012)		●	●	●
Currò et al. (2015)		●		
Darlington et al. (2018)				●
Das et al. (2021)				●
Daumer et al. (2005)				●
Dayama et al. (2020)				●
De Oliveira et al. (2016)				●
Espigado et al. (2003)	●			
Evdoshenko et al. (2011)				●
Fagius et al. (2009)	●			
Farge et al. (2009)				●
Fassas et al. (2000)	●		●	
Fassas et al. (2002)	●			●
Giedraitiene et al. (2020)				●
Gualandi et al. (2007)				●
Guillaume-Jugnot et al. (2019)				●
Guimarães et al. (2010)				●

Hamerschlak et al. (2010)		●	●	●
Haußler et al. (2021)				●
Karnell et al. (2017)				●
Kozak et al. (2001)	●			
Krasulova et al. (2010)			●	●
Kvistad et al. (2020)				●
Mancardi et al. (2012)		●	●	●
Mancardi et al. (2015)		●		
Mariottini et al. (2019)				●
Massey et al. (2017)				●
Moore et al. (2018)				●
Muraro et al. (2017)				●
Murrieta-Álvarez et al. (2021)				●
Nash et al. (2003)	●	●	●	
Nash et al. (2017)			●	●
Ni et al. (2006)	●		●	●
Nicholas et al. (2021)				●
Openshaw et al. (2000)	●			
Ruiz-Argüelles et al. (2019)				●
Saccardi et al. (2005)	●	●	●	●
Saiz et al. (2004)	●		●	●
Samijn et al. (2006)	●	●		●

Shevchecko et al. (2008)	●	●		
Shevchenko et al. (2015)			●	●
Sousa et al. (2015)				●
Su et al. (2006)				●
Tolf et al. (2019)				●
Wiberg et al. (2020)				●
Xu et al. (2006)	●	●		
Xu et al. (2011)			●	●
Zhukovsky et al. (2020)				●

M-A: meta-analyses; MS: multiple sclerosis; SR: systematic reviews.

Table 2. Characteristics of Meta-Analyses on the Use of Autologous HCT for MS

Study	Dates	Studies	Participants	N (range)	Follow-up
Reston et al. (2011) (4)	Through Feb 2009	1 database 13 cohort	Patients with progressive and treatment-refractory MS	428 (5 to 169)	Median: 24 months
Sormani et al. (2017) (5)	1995 to 2016	1 RCT 14 cohort	Patients with severe and treatment-refractory MS	764 (7 to 178)	Median: 42 months
Ge et al. (2019) (6)	Through 2017	18 uncontrolled observational studies	Patients with severe and refractory MS	732 (14 to 145)	Median: 48 months
Nabizadeh et al. (2022) (7)	Through Feb 2022	7 RCT 1 case series 42 cohort	Patients with MS	4831 (12 to 617)	NR

HCT: hematopoietic cell transplantation; N: number; RCT: randomized controlled trial; MS: multiple sclerosis; NR: not reported.

Table 3. Results of Meta-Analyses on the Use of Autologous HCT for Multiple Sclerosis

Study							
Reston et al. (2011) (4)	**N**	**Median follow up**	**PFS, % (95% CI)**	**Sub-population**	**N**	**TRM, N (%)**	**Non-TRM, N (%)**

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 et al. (2019) (6)	**N**	**Median follow-up**	**PFS, % (95% CI)**	**DAFS, % (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 et al. (2017) (5)	**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 et al. (2022) (7)	**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 (91 to 96)	68 (59 to 77)

ARR: annualized relapse rate; CI: confidence interval; EDSS: Expanded Disability Status Scale; EFS: event-free survival; Gd+: gadolinium-enhancing; DAFS: disease activity–free survival; NR: not reported; OM: overall mortality; HCT: hematopoietic cell transplantation; N: number; PFS: progression-free survival; PR: progression rate; Pts: patients; RRMS: relapsing remitting multiple sclerosis; TRM: treatment-resistant mortality; OS: overall survival; SMD: standardized mean difference.

[a] pooled TRM defined as number of deaths within 100 days of transplant/number of transplants.

[b] OM defined as total number 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 4 years posttreatment. Eligibility for the trial was limited to the following criteria: secondary progressive or 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% CI, 0.10 to 0.48, p<.001). Among secondary outcomes, the ARR was significantly lower in the HCT group (19%) compared with the conventional therapy group (60%; p<.03). There was no statistically significant difference between groups in the rate of disease progression (defined as increase of >1 point in 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 an RCT of nonmyeloablative HCT compared to continued disease-modifying therapy on disease progression for patients with RRMS. (10) Between 2005 and 2016, with final follow-up in 2018, 110 patients with RRMS were randomized to receive HCT plus cyclophosphamide and antithymocyte globulin (n=55) or disease-modifying therapy of higher efficacy or a different class than disease-modifying therapy taken in the previous year (n=55). To be eligible, the participants had to have at least 2 relapses with disease-modifying therapy in the prior year and an EDSS of 2.0 to 6.0 (EDSS score range 0 to 10, with 10 being 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 disease-modifying therapy 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 to 48 months) in the disease-modifying therapy group (hazard ratio [HR], 0.07; 95% CI, 0.02 to 0.24). For the HCT group, the proportion of patients with disease progression was 1.92% (95% CI, 0.27% to 12.9%) at 1 year and 2 years, and by 4 and 5 years it was 9.71% (95% CI, 3.0% to 28.8%). Disease progression for the disease-modifying therapy group was 24.5% (95% CI, 14.7% to 39.1%) at 1 year, and 75.3% (95% CI, 60.4% to 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 disease-modifying therapy 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 disease-modifying therapy in prolonging time to disease progression in patients with RRMS. Study limitations included sample size, option to cross over from disease-modifying

therapy to HCT mid-study, and the exclusion of other chemotherapy drugs used in the disease-modifying therapy 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 4). (11) PFS and transplant-related mortality are presented in Table 5. 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 a RIC regimen with different types of MS (Tables 4 and 5). (12) Patients underwent early, conventional, and salvage/late transplantation. Efficacy was evaluated based on clinical and QOL outcomes. All patients, except 1, responded to treatment. At long-term follow-up (mean, 46 months), the overall clinical response regarding 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); another 35 patients had a shorter follow up, and the remainder were lost to follow-up. (13) Thirty (47%) of the 64 patients improved by at least 0.5 points 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 4). (14) Thirty-six patients had secondary progressive disease and 25 had RRMS. Clinical and MRI outcomes were reported (Table 5). 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 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 1 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 of more than 7 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 4 and 5). (15) Patients were treated with nonmyeloablative HCT between 2003 and 2014. Six patients were not included in the outcome analysis (lost to follow-up and nonreproducible neurologic findings). The remaining 145 patients were followed for a median of 2 years (range, 6 months to 5 years). Change in 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 a 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 a disease with high relapse frequency, and who failed conventional therapy) (Tables 4 and 5). (16) Patients underwent autologous HCT. At the 5-year follow-up, relapse-free survival (RFS) was 87%, and the EDSS score PFS (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 4). (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 5. 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. Moreover, 33% of the patients 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 trial were published by Nash et al. (2017) (Tables 4 and 5). (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 RFS (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 4). (19) Data was collected from 25 centers in 13 European countries. Results are presented in Table 5. Factors associated with neurological progression included age, progressive versus relapsing MS, and $\geq$2 previous therapies.

Kvistad et al. (2019) performed a retrospective cohort study of 30 patients in Norway with RRMS treated with HCT between 2015-2018 (Table 4). (20) Results for PFS and TRM are

presented in Table 5. 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 RRMS, secondary progressive MS, or primary progressive MS treated with HCT between 1997 and 2019 (Table 4). (21) Results for the primary outcome of disability worsening-free survival are presented in Table 5. 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 U.S. between 2003 and 2019 (Table 4). (22) Results for PFS and TRM are presented in Table 5. Additionally, RFS at 5 years for patients with RRMS and secondary-progressive MS was 80.1% and 98.1%, respectively.

Silfverberg et al. (2024) performed a retrospective cohort study of 174 patients with RRMS from the Swedish MS registry who were treated with HCT before January 2020 (Table 4). (23) Results for PFS are presented in Table 5. At 5 and 10 years, RFS for patients with RRMS was 73% and 65%, respectively.

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

Study	Study Design	Country	Participants	N	Median years (range) follow-up
Fassas et al. (2011) (11)	Case series	Greece	Patients with aggressive MS treated with HCT	35	11 (2 to 15)
Shevchenko et al. (2012) (12) Shevchenko et al. (2015) (13)	Case series	Russia	Patients with progressive MS or RRMS treated with HCT	99	4 (NR)
Mancardi et al. (2012) (14)	Case series	Italy	Patients with severe MS treated with HCT	74	4 (0.8 to 10)
Burman et al. (2014) (16)	Case series	Sweden	Patients with aggressive MS treated with HCT	41	4 (1 to 9)
Burt et al. (2015) (15)	Case series	United States	Patients with RRMS treated with HCT	151	2 (0.5 to 5)
Atkins et al. (2016) (17)	Case series	Canada	Patients with relapsing MS treated with HCT	24	6.7 (4 to 13)
Nash et al. (2017) (18)	Case series	United States	Patients with RRMS or progressive MS treated with HCT	24	5.2 (1 to 6)

Muraro et al. (2017) (19)	Retrospective cohort	Europe (13 countries)	Patients with aggressive treatment-refractory MS treated with HCT	281	6.6 (0.2 to 16)
Kvistad et al. (2019) (20)	Retrospective cohort	Norway	Patients with RRMS or progressive MS treated with HCT	30	26 (11 to 48)
Boffa et al. (2021) (21)	Retrospective cohort	Italy	Patients with RRMS, secondary progressive MS, or primary progressive MS treated with HCT	210	6.2 (NR)
Burt et al. (2021) (22)	Retrospective cohort	United States	Patients with RRMS or newly diagnosed secondary progressive MS treated with HCT	507	3 (NR)
Silfverberg et al. (2024) (23)	Retrospective cohort	Sweden	Patients with RRMS treated with HCT	174	5.5 (3.4 to 7.5)

HCT: hematopoietic cell transplantation, MS: multiple sclerosis, N: number; RRMS: relapsing-remitting multiple sclerosis; NR: not reported.

Table 5. Results of Observational Studies of HCT for MS (≥2 years Follow-Up)

Study	Follow-up	PFS, % (95% CI)	TRM, N (%)
Fassas et al. (2011) (11)	15 years	All: 25 (NR) Active MRI lesions: 44 (NR) No active MRI lesions: 10 (NR)	2 (5.7%)
Shevchenko et al. (2012) (12) Shevchenko et al. (2015) (13)	8 years	80 (68 to 88)	0
Mancardi et al. (2012) (14)	4 years	NR	2 (2.7)
Burman et al. (2014) (16)	5 years	68 (NR)	0
Burt et al. (2015) (15)	2 years 4 years	92 (85 to 96) 87 (78 to 93)	0
Atkins et al. (2016) (17)	3 years	70 (47 to 84)	1 (4.2)
Nash et al. (2017) (18)	5 years	91 (75 to 97)	0
Muraro et al. (2017) (19)	5 years	All: 46 (42 to 54) Relapsing: 73 (57 to 88)	8 (2.8)
Kvistad et al. (2019) (20)	2 years	7 (NR)	0
Boffa et al. (2021) (21)	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 et al. (2021) (22)	4 years	RRMS: 95 Secondary progressive MS: 66	1 (0.19)

Silfverberg et al. (2024) (23)	up to 10 years	5 years: 73 (66 to 81) 10 years: 65 (57 to 75)	0

[a] This study measured disability worsening-free survival.
CI: confidence interval; HCT: hematopoietic cell transplantation, MRI: magnetic resonance imaging; MS: multiple sclerosis, N: number; NR: not reported; PFS: progression-free survival: TRM: treatment-resistant mortality; RRMS: relapsing-remitting multiple sclerosis.

Section Summary: Multiple Sclerosis

Evidence for the use of HCT in patients with MS consists of RCTs, systematic reviews, and many single-arm studies. Several systematic reviews for HCT are available, but the vast majority of data comes from observational studies without a control group, prohibiting conclusions comparing HCT with disease-modifying therapy. 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 patients 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, RFS, disease activity-free survival, disability worsening-free survival, disease stabilization, number of new lesions, and improvements in EDSS scores. While improvements were seen in all outcomes compared with baseline, there were no comparative treatments. Adverse event rates were high, and most studies reported treatment-related death rates ranging from 0 to 4%.

Systemic Sclerosis (Scleroderma)

Clinical Context and Therapy Purpose

The purpose of HCT in individuals who have systemic sclerosis (scleroderma) 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 policy.

Populations

The relevant population of interest is individuals with systemic sclerosis or scleroderma.

Interventions

The therapy being considered is HCT.

Comparators

Comparators consist of conventional medical therapy. Most individuals with autoimmune disorders such as systemic sclerosis or scleroderma 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 OS, symptoms, health status measures, QOL, TRM, and treatment-related morbidity. Specific outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

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 a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-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.

Systematic Reviews

A review by Milanetti et al. (2011) summarized eight phase 1 and 2 clinical studies using autologous HCT to treat systemic sclerosis. (24) 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. (25) 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 (EFS) and all studies reported improvements in modified Rodnan skin score (mRSS). 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. (26) 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 TRM 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. (27) 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. (28) There were 3 RCTs (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 2 trial (Trial of High Dose Cyclophosphamide and Rabbit Antithymocyte Globulin [rATG] With Hematopoietic Stem Cell Support in Patients With Systemic Scleroderma: A Randomized Trial [ASSIST]; Burt et al. [2011]) evaluated the safety and efficacy of autologous nonmyeloablative HCT compared with the standard of care (cyclophosphamide) (Table 6). (29) The primary outcome was an 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 (FVC) of more than 10% (Table 7). Patients in the control group with disease progression (>25% increase in mRSS or decrease of >10% in FVC) despite treatment with cyclophosphamide could switch to HCT 12 months after enrollment. Patients allocated to HCT (n=10) improved at or before the 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<.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 FVC, with the longest follow-up of 60 months. Seven patients allocated to 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 FVC 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 a follow-up to 2 years after HCT suggested that the improvements in mRSS (p<0.001) and FVC (p<0.03) persisted.

Results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published by van Laar et al. (2014) (Tables 6 and 7). (30) The ASTIS trial was a phase 3 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 endpoint was event-free survival (EFS), 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 endpoints included TRM, toxicity, and disease-related changes in mRSS, organ function, body weight, and QOL 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 trial 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 nonadherence. 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 was allowed at the discretion of the investigators, adding further uncertainty to the results. Of the 53 primary endpoint 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 were in the control group (23 deaths, 8 irreversible organ failures [7 of whom died later]; 19 patients died of disease progression, 4 of cardiovascular disease, 5 of malignancy, 2 of other causes). The data showed patients treated with HCT experienced more events in the first year but appeared to have better long-term EFS than the controls, with Kaplan-Meier curves for OS crossing at about 2 years after treatment with the OS rate at that time estimated at 85%. According to the Kaplan-Meier curves, at 5 years, OS rate was an estimated at 66% in the control group and an estimated at 80% in the HCT group (p-value unknown). Time-varying HRs (modeled with treatment by time interaction) for EFS were 0.35 (95% CI, 0.15 to 0.74) at 2 years and 0.34 (95% CI, 0.16 to 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 and 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 6). (31) 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, FVC, Disability Index of the Health Assessment Questionnaire, and the mRSS. There was more percent pairwise comparisons favoring HCT over cyclophosphamide alone at 4- and 4.5-years follow-up (Table 7). 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 2 treatment groups: arrhythmia, pericardial effusion, renal crisis, and myositis. Comparisons in mortality rates are presented in Table 7.

Table 6. Characteristics of RCTs of HCT for Systemic Sclerosis

Study, Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Burt et al. (2011) (29), ASSIST	United States	1	2006 to 2009	Adult patients <60 years with diffuse SSc; mRSS ≥15; internal organ involvement	High-dose intravenous cyclophosphamide 200 mg/kg; intravenous rabbit antithymocyte-globulin 6.5 mg/kg total dose; autologous HCT (n=10)	6 monthly treatments with intravenous pulsed cyclophosphamide (1000 mg/m^2) (n=9)
van Laar et al. (2014) (30), 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 antithymocyte-globulin 7.5 mg/kg total dose; autologous HCT (n=79)	12 monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m^2) (n=77)
Sullivan et al. (2018) (31), 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); autologous HCT (n=36)	12 monthly treatments with intravenous pulsed cyclophosphamide (n=39)

HCT: hematopoietic cell transplantation; mRSS: modified Rodnan skin scores; n: number; RCT: randomized controlled trial; SSc: systemic sclerosis; cGy: centigray; mg/kg: milligram/killigram; mg/m^2: milligrams per square meter.

Table 7. Results of RCTs of HCT for Systemic Sclerosis

Study	**Efficacy Outcomes**				**Adverse Events**	**TRM n (%)**
Burt et al. (2011) (29), ASSIST	**mRSS at 1 yr mean (SD)**		**FVC at 1 yr Mean % (SD)**			
aHCT	15 (7.9)		74 (15.7)		NR	0
cyclophosphamide	22 (14.2)		61 (19.8)		NR	0
van Laar et al. (2014) (30), ASTIS	**Events 1 yr**	**Events 4 yrs**	**Deaths 1 yr**	**Deaths 4 yrs**	**≥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 et al. (2018) (31), SCOT	**Global Rank Composite Score, at 4 yrs**		**Global Rank Composite Score, at 4.5 yrs**		**≥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 yrs: 10 (28)		At 4.5 yrs: 6 (17)			
cyclophosphamide	At 4 yrs: 20 (51)		At 4.5 yrs: 11 (28)			
p-value	0.06		0.28			

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

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. (32) 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 years), 81% (n=21/26) of the patients demonstrated a clinically beneficial response. Skin sclerosis was measured with a mRSS, and a significant (i.e., >25%) decrease (i.e., improvement) was achieved in 19 of 26 patients after 1 year and in 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 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 Status score of 0 increased to 56% from 4% at baseline. The estimated survival rate at 5 years was 96.2% (95% CI, 89% to 100%) and at 7 years was 84.8% (95% CI, 70.2% to 100%); and the EFS rate (survival without mortality, relapse, or progression of systemic sclerosis resulting in major organ dysfunction) was 64.3% (95% CI, 47.9% to 86%) at 5 years and 57.1% (95% CI, 39.3% to 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%. (33)

Nash et al. (2007) reported on 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. (34) 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, 1-8 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 OS and PFS rates 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. (35) The main outcome variable was a response to treatment (reduction of mRSS by 25%) at 6 months. Secondary endpoints were transplant-related mortality and PFS. At 6 months, significant skin and lung function improvement assessed on the mRSS was achieved in 78.3% of patients. The 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. The PFS rate 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 2012 and 2016. (36) After a median follow-up of 24 months after HCT, the primary endpoint of PFS was 81.8%, and secondary endpoints of OS, 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. (37) 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 mRSS 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 mRSS 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
Clinical Context and Therapy Purpose
The purpose of HCT in individuals who have SLE 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 policy.

Populations
The relevant population of interest is individuals with SLE.

Interventions
The therapy being considered is HCT.

Comparators
Comparators consist of conventional medical therapy. Most individuals with autoimmune disorders such as SLE 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 include OS, symptoms, QOL, TRM, and treatment-related morbidity. Specific outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

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 a preference for RCTs;

- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-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.

Systematic Review

Leone et al. (2018) conducted a systematic review of clinical and laboratory studies using autologous HCT for patients with SLE. (38) 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 (I^2=87%). The only pooled analysis conducted was on 5 studies reporting deaths, resulting in overall mortality of 8.3% in a mean follow-up of 36 months.

Case Series

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 on the largest single-center series using HCT for SLE in the United States. (39) Between 1997 through 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 the use of cyclophosphamide. Patients underwent autologous HCT following a lymphoablative conditioning regimen. Two patients died after mobilization, yielding a TRM of 4% (2/50). After a mean follow-up of 29 months (range, 6 months to 7.5 years), the 5-year OS rate was 84%, and the probability of disease-free survival (DFS) was 50%. Several parameters of SLE activity improved, including renal function, SLE Disease Activity Index score, antinuclear antibody, anti-double stranded DNA, complement C3 and C4 levels, and carbon monoxide diffusion lung capacity. The investigators suggested these results justified 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 HCT for 17 patients with SLE after 7 years follow-up. (40) The OS and PFS rates were used to assess the efficacy and toxicity 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% and 64.7%, respectively. The principal adverse events included allergy, infection, elevated 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 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. (41) 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 had died, and 1 had active disease.

Cao et al. (2017) reported on 22 patients with SLE who underwent autologous peripheral blood HCT. (42) At 5-year follow-up, PFS was 68% and OS was 95%. At last follow-up, 10 patients had relapsed. Adverse events included infections, secondary autoimmunity, lymphoma, and malignancy. The authors noted 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. (43) Outcomes were measured at 6 months and yearly through 5 years. Disease remission was achieved by 24 patients. The SLE Disease Activity Index and QOL 36-Item Short Form Health Survey 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: SLE

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

Clinical Context and Therapy Purpose

The purpose of HCT in individuals who have juvenile idiopathic arthritis (JIA) or rheumatoid arthritis (RA) 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 policy.

Populations

The relevant population of interest is individuals with JIA or RA.

Interventions

The therapy being considered is HCT.

Comparators

Comparators consist of conventional medication therapy or biologic therapy. Most individuals with autoimmune disorders such as JIA or RA 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 OS, symptoms, QOL, TRM, and treatment-related morbidity. Specific outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

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 a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-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.

Registry Data
A review article by Saccardi et al. (2008) on HCT for autoimmune diseases has summarized the experience with JIA and RA as follows. (44) More than 50 patients with JIA 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 RA 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 allo-HCT. (45) Patients experienced significant improvements in arthritis and QOL, with 11 children achieving drug-free remission at last follow-up. At a median follow-up of 29 months, 1 patient died of probable sepsis following elective surgery and 1 died of invasive fungal infection, for a treatment-related mortality rate of 12.5%.

Section Summary: JIA or RA
Evidence for the use of HCT on patients with JIA consists of data from an EBMT Registry (N>50) and a case series. 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 (CIDP)

Clinical Context and Therapy Purpose

The purpose of HCT in individuals who have chronic inflammatory demyelinating polyneuropathy 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 policy.

Populations

The relevant population of interest is individuals with chronic inflammatory demyelinating polyneuropathy.

Interventions

The therapy being considered is HCT.

Comparators

Comparators consist of conventional medication therapy. Most individuals with autoimmune disorders such as chronic inflammatory demyelinating polyneuropathy 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

General outcomes of interest are OS, symptoms, health status measures, QOL, TRM, and treatment-related morbidity. Specific outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

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 a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-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.

Systematic Reviews

Several review articles have summarized experience with HCT in the treatment of CIDP. (46-48) In general, the evidence includes a few case reports describing outcomes for 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 8). (49) 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 9. 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 8. Characteristics of Observational Studies of HCT for CIDP

Study	Study Design	Country	Participants	N	Follow-Up, median years (range)
Burt et al. (2020) (49)	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; HCT: hematopoietic cell transplantation; N: number.

Table 9. Results of Observational Studies of HCT for Chronic Inflammatory Demyelinating Polyneuropathy

Study	OS, % (95% CI)	Medication-free remission (%)	Ambulation-free assistance (%)
Burt et al. (2020) (49)	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; HCT: hematopoietic cell transplantation.

Section Summary: CIDP

Evidence for the use of HCT to treat patients with CIDP 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

Clinical Context and Therapy Purpose

The purpose of HCT in individuals who have type 1 diabetes 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 policy.

Populations

The relevant population of interest is individuals with type 1 diabetes.

Interventions

The therapy being considered is HCT.

Comparators

Comparators consist of conventional medication therapy. Most individuals with type 1 diabetes are managed with insulin therapy.

Outcomes

General outcomes of interest are OS, symptoms, health status measures, QOL, TRM, and treatment-related morbidity. Specific outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

Follow-up for 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 a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-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.

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 10 and 11). (50) 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 Table 12. 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 hemoglobin A1c (HbA_{1c}) 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 10 and 11). (51) The literature search, conducted through August 2015, identified 22 studies for inclusion; study design of included studies was not consistently reported. Fifteen of the studies (n=300 patients) involved patients with type 1 diabetes; 7 studies (n=224 patients) involved patients with type 2 diabetes. Results for the cohort of patients with type 1 diabetes are presented in Table 12. 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 13 presents comparisons of C-peptide levels and HbA_{1c} 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 are needed.

Table 10. Comparison of Studies Included in Systematic Reviews of Studies of Patients with Diabetes Treated with HCT

Study	Sun et al. (2020) (50)	El-Badawy and El-Badri (2011) (51)
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 11. Summary of Systematic Reviews of Studies of Patients with Diabetes Treated with HCT

Study	Dates	Studies	Participants	N (range)	Duration
Sun et al. (2020) (50)	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) (51)	To August 2015	22	Patients with type 1 diabetes (15 studies; n=300); patients with type 2 diabetes (7 studies; n=224)	524 (8 to 118)	6 to 48 months

HCT: hematopoietic cell transplantation; RCT: randomized controlled trial; n/N: number.

Table 12. 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 et al. (2020) (50)					
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) (51)					
Total N	199	193	NR	NR	NR
Pooled effect (95% CI)	SMD versus baseline, -0.57 (-0.79 to -0.35)	SMD versus 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; MD: mean difference; NR: not reported; SMD: standardized mean difference; HCT: hematopoietic cell transplantation; RR: relative risk; HbA_{1c}: hemoglobin A1c; N: number.

Table 13. Standardized 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 Pts	SMD (95% CI) C-Peptide	No. of Studies	No. of Pts	SMD (95% CI) HbA_{1c}
Type 1						
UCB	4	56	1.07 (0.67 to 1.48)	4	61	0.05 (-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). (51)

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; No: number; Pts: patients; SMD: standard mean difference; UCB: umbilical cord blood; UC-MSC: umbilical cord mesenchymal stem cells.

Case Series

Several case series have 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. (52) 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 A_{1c} 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. (53) 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 of a 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 1 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. (54) Adverse events include neutropenic fever in 12 (50%) patients. 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-analyses. The meta-analyses revealed that HCT may improve HbA_{1c} 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 1 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

Clinical Context and Therapy Purpose

The purpose of HCT in individuals who have other autoimmune diseases 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 policy.

Populations

The relevant population of interest is individuals with other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis).

Interventions

The therapy being considered is HCT.

Comparators

Comparators consist of conventional medication 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

General outcomes of interest are OS, symptoms, health status measures, QOL, TRM, and treatment-related morbidity. Specific outcomes of interest include PFS, OS, improvement in clinical symptoms, adverse events, and TRM.

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 a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-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.

Crohn Disease

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

Hawkey et al. (2015) have conducted the only RCT (ASTIC trial; NCT00297193) evaluating the effect of HCT on Crohn disease. (55) 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 treated patients and the control patients who underwent deferred HCT. (56) Outcomes were 3-month steroid-free clinical remission at 1 year and degree of endoscopic healing at 1 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 were experienced in 23 of 40 patients.

Lindsay et al. (2024) conducted another RCT (ASTIClite) evaluating the effects of reduced intensity conditioning with HCT on Crohn disease. (57) The primary endpoint was endoscopic healing without surgery or death at 52 weeks. However, the trial was ended early due to unexpected serious adverse reactions in six (46%) patients in the intervention group, including renal failure due to proven thrombotic microangiopathy and death. At week 48, endoscopic healing without surgery or death occurred in 3 (43%) of 7 participants in the intervention group and in 0 of 6 in the control group with available data.

Brierley et al. (2018) published a review of patients in the EBMT Registry undergoing autologous HCT for Crohn disease (n=82) who had failed a median of 6 lines of drug therapy. (58) At a 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 (e.g., 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). (59) 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 2 RCTs 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 a recurrence of symptoms within 1 year.

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

Summary of Evidence

For individuals with multiple sclerosis (MS) who receive hematopoietic cell transplantation (HCT), the evidence includes randomized controlled trials (RCTs), systematic reviews, and several nonrandomized studies. Relevant outcomes are overall survival (OS), health status measures, quality of life (QOL), and treatment-related mortality (TRM) and morbidity. Systematic reviews are primarily comprised of observational data. One RCT compared HCT with mitoxantrone, and the trial reported intermediate outcomes (number of new T2 magnetic resonance imaging [MRI] lesions); the group randomized to HCT developed significantly fewer lesions than the group receiving conventional therapy. The other RCT compared nonmyeloablative HCT results in patients with continued disease-modifying therapy and found a benefit to HCT in prolonged time to disease progression. The findings of the nonrandomized studies revealed improvements in clinical parameters following HCT compared with baseline. Adverse event rates were high, and most studies reported treatment-related deaths. Controlled trials (with appropriate comparator therapies) reporting on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes systematic reviews, 3 RCTs, and observational studies. Relevant outcomes are OS, symptoms, health status measures, QOL, and TRM 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 >15, and internal organ involvement. Patients with severe and irreversible organ involvement were excluded from the trials. Short-term results of the RCTs show higher rates of adverse events and TRM among patients receiving autologous HCT compared with patients receiving chemotherapy alone. However, long-term improvements (4 years) in overall mortality and clinical outcomes such as modified Rodnan skin scores and forced vital capacity 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 3 RCTs, statistical significance was found only in the larger RCT. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with systemic lupus erythematosus (SLE) who receive HCT, the evidence includes a systematic review and case series. Relevant outcomes are OS, symptoms, QOL, and treatment-related mortality and morbidity. Studies were heterogeneous in conditioning regimens and source of cells. The largest series (n=50) reported an overall 5-year survival rate of 84% and the probability of disease-free survival (DFS) was 50%. Additional data are needed

from controlled studies to demonstrate efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with juvenile idiopathic or rheumatoid arthritis who receive HCT, the evidence includes registry data and a case series. Relevant outcomes are OS, symptoms, QOL, 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 that the technology results in an improvement in the net health outcome.

For individuals with chronic inflammatory demyelinating polyneuropathy who receive HCT, the evidence includes a recent observational study and case reports. Relevant outcomes are OS, symptoms, health status measures, QOL, and treatment-related mortality and morbidity. Additional data is needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with type 1 diabetes who receive HCT, the evidence includes case series and 2 meta-analyses. Relevant outcomes are OS, symptoms, health status measures, QOL, and treatment-related mortality and morbidity. While a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high. The meta-analyses revealed that HCT may improve HbA_{1c} 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 1 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 in treating diabetes; those factors are heterogeneity in the stem cell types, cell number infused, and infusion methods. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes 2 RCTs and small retrospective studies, and case series. Relevant outcomes are OS, symptoms, health status measures, QOL, and treatment-related mortality and morbidity. The RCT was conducted on patients with Crohn disease. At 1-year follow-up, 1 patient in the control group and 2 patients in the HCT group achieved remission. Data is needed from additional controlled studies to demonstrate efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net outcome.

Practice Guidelines and Position Statements

American Society for Transplantation and Cellular Therapy

In 2020, the American Society for Transplantation and Cellular Therapy (formerly the American Society for Blood and Marrow Transplantation) published consensus guidelines on the use of hematopoetic cell transplantation (HCT) to treat specific conditions in and out of the clinical

trial setting. (60) Table 14 summarizes recommendations for specific indications addressed in this guideline.

Table 14. Recommendations for the Use of HCT to Treat Autoimmune Diseases

Indications for HCT in Pediatric Patients (Generally <18 years)	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 years		
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 (C): 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 indication (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. However, single-center, 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."

Medicare National Coverage

There are numerous autoimmune diseases, and the Centers for Medicare & Medicaid Services has not issued a national coverage determination for stem cell transplantation for each disease.

A general national coverage determination for stem cell transplantation (110.23; formerly 110.8.1) states as listed in Table 15. (61)

Table 15. Nationally Covered and Noncovered Indications for HCT

Covered and Noncovered Indications
Nationally covered indications
Allogeneic HCT
“Effective...1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary”
“Effective...1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome”
"Effective...2024, allogeneic hematopoietic stem cell transplant using bone marrow, peripheral blood or umbilical cord blood stem cell products for Medicare patients with myelodysplastic syndromes who have prognostic risk scores of: ≥1.5 (intermediate-2 or high) using the International Prognostic Scoring System (IPSS), or ≥4.5 (high or very high) using the International Prognostic Scoring System-Revised (IPSS-R), or ≥0.5 (high or very high) using the Molecular International Prognostic Scoring System (IPSS-M)"
Autologous HCT
"Effective...1989, [autologous HCT] is considered reasonable and necessary … for the following conditions and is covered under Medicare for patients with: • Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched; • Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response; • Recurrent or refractory neuroblastoma; or, • Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor."
"Effective...2000, single [autologous HCT] 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.”
"Effective...2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with [autologous HCT] 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%.”
Nationally noncovered indications
Allogeneic HCT

"Effective...1996, through January 26, 2016, allogeneic [HCT] is not covered as treatment for multiple myeloma."
Autologous HCT
"Insufficient data exist to establish definite conclusions regarding the efficacy of [autologous HCT] 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 transplantation (multiple rounds of [autologous HCT]) for patients with multiple myeloma; • Effective...2000, non primary AL amyloidosis; and, • Effective...2000 through March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older. In these cases, [autologous HCT] is not considered reasonable and necessary...and is not covered under Medicare."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 16.

Table 16. Summary of Key Trials

NCT Number	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	1000	Dec 2025
NCT03477500	Randomized Autologous Hematopoietic Stem Cell Transplantation Versus Alemtuzumab for Patients with Relapsing Remitting Multiple Sclerosis (RAM-MS)	100	Mar 2026
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 (MASCT - CD)	50	Apr 2026
NCT00716066	High-Dose Immunosuppressive Therapy Using Carmustine, Etoposide, Cytarabine, and Melphalan (BEAM) + Thymoglobulin	53	Jan 2030

	Followed by Syngeneic or Autologous Hematopoietic Cell Transplantation for Patients With Autoimmune Neurologic Diseases		
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
Unpublished			
NCT03069170[a]	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
NCT01895244	High-dose Chemotherapy and Transplantation of 43+ Selected Stem Cells for Progressive Systemic Sclerosis - Modification According to Manifestation	44	Jun 2024

NCT: national clinical trial.

[a] denotes industry sponsored or co-sponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
08/01/2025	Document updated with literature review. Coverage reorganized with movement of some criteria to Policy Guidelines; no change to policy intent. References 23 and 57 added; others updated.
11/15/2024	Reviewed. No changes.
01/01/2024	Document updated with literature review. Coverage unchanged. References 4-8, 21-22, 26-27, 58-59 added; others removed.
04/15/2022	Reviewed. No changes.
09/15/2021	Document updated with literature review. Coverage unchanged. Added references: 5, 8, 19, 30-31, 43-44, 53, and 57.
07/15/2020	Reviewed. No changes.
08/01/2019	Document updated with literature review. The following change was made to Coverage: Statement for systemic sclerosis was changed from "experimental, investigational and/or unproven to "medically necessary" when criteria are met. Added references: 7, 16, 18-19, 22, 27, 31-32, 34, 39, 42, 44-46, 49-51, 54-55. Title changed from "Hematopoietic Stem-Cell Transplantation for Autoimmune Disorders".
08/15/2018	Reviewed. No changes.
12/15/2017	Document updated with literature review. Coverage unchanged.
06/01/2016	Document updated with literature review. Coverage unchanged.
05/01/2015	Document updated with literature review. Chronic inflammatory demyelinating polyneuropathy was added to the listing of experimental, investigational and/or unproven indications. The policy title changed from Stem-Cell Transplant for Autoimmune Disorders.