Hematopoietic Cell Transplantation for Autoimmune Diseases

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I. Description

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

For individuals with multiple sclerosis who receive HCT, the evidence includes a randomized controlled trial (RCT) and several case series. Relevant outcomes are overall survival, health status measures, quality of life, and treatment-related mortality and morbidity. The phase 2 RCT compared HCT with mitoxantrone, and the trial reported intermediate outcomes (number of new T2 magnetic resonance imaging lesions); the group randomized to HCT developed significantly fewer lesions than the group receiving conventional therapy. The findings of the case series 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 the effects of the technology on health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes RCTs and observational studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. The results of the ASTIS trial (N=156) have suggested high-dose chemotherapy plus autologous HCT might improve survival among patients with diffuse cutaneous systemic sclerosis compared with pulsed intravenous cyclophosphamide. However, analysis of the internal validity of the trial using U.S. Preventive Services Task Force criteria showed fatal flaws and a poor study rating due to attrition in the control group that could have skewed the survival curve to show better survival for HCT recipients than for controls. A smaller RCT (N=19) found that the rate of improvement at 12 months was significantly higher in the HCT group than in the conventional therapy group. Data from these trials,

however, are inconclusive, and additional studies are needed to confirm safety and efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic lupus erythematosus who receive HCT, the evidence includes case series. Relevant outcomes are overall survival, symptoms, quality of life, and treatment-related mortality and morbidity. Several case series (total N=91 patients) have been published. The largest series (N=50) reported an overall 5-year survival rate of 84% and the probability of disease-free survival was 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

For individuals with type 1 diabetes who receive HCT, the evidence includes case series and a meta-analysis of 22 studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. While a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high. A meta-analysis further revealed that HCT is more effective in patients with type 1 diabetes and when HCT is administered soon after the diagnosis. Certain factors limit the conclusions that can be drawn about the overall effectiveness of HCT in treating diabetes; those factors are: heterogeneity in the stem cell types, cell number infused, and infusion methods. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with other autoimmune diseases (eg, Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes small retrospective studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Background

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

The pathogenesis of autoimmune diseases is not well-understood but appears to involve underlying genetic susceptibility and environmental factors that lead to loss of self-tolerance, culminating in tissue damage by the patient's own immune system (T cells).

Treatment
Immune suppression is a common treatment strategy for many of these diseases, particularly the rheumatic diseases (e.g., RA, SLE, and 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 hematopoietic cell transplantation (HCT). The primary concept underlying use of HCT for these diseases is this: ablating and "resetting" the immune system can alter the disease process, first inducing a sustained remission that possibly leads to cure.

Hematopoietic Cell Transplantation
HCT refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically "naïve" and thus, are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the class I and class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Autologous Stem-Cell Transplantation for Autoimmune Diseases
The goal of autologous HCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablative) and generate new self-tolerant lymphocytes. This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablative), as is often performed in autologous HCT for hematologic malignancies. However, there is currently no standard conditioning regimen for autoimmune diseases and both lymphoablative and myeloablative regimens are used. The efficacy of the different conditioning regimens has not been compared in clinical trials.

Currently, for autoimmune diseases, autologous transplant is preferred over allogeneic, in part because of the lower toxicity of autotransplant relative to allogeneic, the GVHD associated with

allogeneic transplant, and the need to administer post-transplant immunosuppression after an allogeneic transplant.

Allogeneic Stem-Cell Transplantation for Autoimmune Diseases
Experience of using allogeneic HCT for autoimmune diseases is currently limited but has two potential advantages over autologous transplant. First, the use of donor cells from a genetically different individual could possibly eliminate genetic susceptibility to the autoimmune disease and potentially result in a cure. Second, there exists a possible graft-versus-autoimmune effect, in which the donor T cells attack the transplant recipient's autoreactive immune cells.

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

II. Criteria/Guidelines

Autologous or allogeneic hematopoietic cell transplantation is not covered as a treatment of autoimmune diseases, including, but not limited to the following as they are not known to improve health outcomes:

- multiple sclerosis
- systemic sclerosis/scleroderma
- systemic lupus erythematosus
- juvenile idiopathic or rheumatoid arthritis
- chronic inflammatory demyelinating polyneuropathy
- type 1 diabetes.

III. Administrative Guidelines

In 2003, CPT centralized codes describing allogeneic and autologous hematopoietic cell transplant services to the hematology section (CPT 38204-38242). Not all codes are applicable for each transplant procedure. For example, Plans should determine whether cryopreservation is performed. A range of codes describe services associated with cryopreservation, storage, and thawing of cells (38208-38215).

CPT Code	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous
38208	Transplant preparation of hematopoietic progenitor cells; thawing of

	previously frozen harvest, without washing, per donor
38209	; thawing of previously frozen harvest with washing, per donor
38210	; specific cell depletion with harvest, T-cell depletion
38211	; tumor cell depletion
38212	; red blood cell removal
38213	; platelet depletion
38214	; plasma (volume) depletion
38215	; cell concentration in plasma, mononuclear, or buffy coat layer
38222	Diagnostic bone marrow; biopsy (ies) and aspiration(s)
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	;autologous transplantation
HCPCS Code	**Description**
Q0083 - Q0085	Chemotherapy, administer code range
J9000-J9999	Chemotherapy drug code range
S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic, and emergency services)
ICD-10-PCS	**Description**
30243G0, 30243X0, 30243Y0	Percutaneous transfusion, central vein, bone marrow or stem cells, autologous, code list
30243G1, 30243X1, 30243Y1	Percutaneous transfusion, central vein, bone marrow or stem cells, nonautologous, code list
07DQ0ZZ, 07DQ3ZZ, 07DR0ZZ, 07DR3ZZ, 07DS0ZZ, 07DS3ZZ	Surgical, lymphatic and hemic systems, extraction, bone marrow, code list

IV. Scientific Background

This evidence review was created in December 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed through November 21, 2017.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the 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.

Recent reviews have summarized the research to date using hematopoietic cell transplantation (HCT) to treat a number of autoimmune diseases.

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 with the clinical indications of multiple sclerosis (MS; n=379), systemic sclerosis (n=207), systemic lupus erythematosus (SLE; n=92), rheumatoid arthritis (n=88), juvenile idiopathic arthritis (n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn disease (n=23).

MULTIPLE SCLEROSIS

Randomized Controlled Trials
A randomized controlled trial (RCT), Autologous Stem Cell Transplantation in Multiple Sclerosis, which compared HCT with mitoxantrone for treatment of MS, was published in 2015 by Mancardi et al.[5] 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 relapsing-remitting multiple sclerosis (RRMS), a documented worsening during the last year, and lack of response to conventional therapy. Twenty-one patients were randomized to autologous HCT (n=9) or medical therapy (mitoxantrone) (n=12). Follow-up data were collected every 6 months for 48 months. Data were not available for 4 patients; missing data were imputed in the intention-to-treat analysis of the primary outcome. The median number of new T2 MRI lesions was 2.5 in the HCT group and 8 in the conventional therapy group (rate ratio, 0.21; 95% confidence interval [CI], 0.10 to 0.48, p<0.001). Among secondary outcomes, the annualized relapse rate was significantly lower in the HCT group (19%) compared with the conventional therapy group (60%; p<0.03). There was no statistically significant difference between groups in the rate of disease progression (defined as increase of >1 point in Expanded Disability Status Scale [EDSS] score if baseline was 3.5 to 5.5 or increase of >0.5 if baseline 5.5 to 6.5) or change in disability status.

Systematic Reviews

A 2011 systematic review evaluated the safety and efficacy of autologous HCT in patients with progressive MS refractory to conventional medical treatment.6 Fourteen studies met inclusion criteria, of which 8 case series met inclusion criteria for the primary outcome of progression-free survival (PFS), with a median follow-up of at least 2 years. The other 6 studies were included for a summary of mortality and morbidity rates. Across the 8 case series, there was substantial heterogeneity. Most patients (77%) had secondary progressive MS, although studies also included patients with primary progressive, progressive-relapsing, and RRMS. Sample sizes across studies ranged between 14 and 26 patients. The studies differed in the types and intensities of conditioning regimens used before HCT, with 5 studies using an intermediate-intensity regimen and three using high-intensity regimens. All studies were rated moderate quality. The estimated rate of long-term PFS for patients receiving an intermediate-intensity conditioning regimen was 79.4% (95% CI, 69.9% to 86.5%) with a median follow-up of 39 months, while the estimate for patients who received a high-dose regimen was 44.6% (95% CI, 26.5% to 64.5%) at a median follow-up of 24 months. Of the 14 studies that reported adverse events, 13 were case series; of the 13, 7 treatment-related deaths were recorded, and 6 non-treatment-related deaths occurred. Of the six non-treatment-related deaths, five were associated with disease progression.

Nonrandomized Studies

A 2012 study by Shevchenko et al reported on the results of a prospective, open-label, single-center study that analyzed the safety and efficacy of autologous HCT with a reduced-intensity conditioning regimen in 95 patients with different types of MS.7 Patients underwent early, conventional, and salvage/late transplantation. Efficacy was evaluated based on clinical and quality of life outcomes. No transplantation-related deaths were observed. All patients, except one, 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 on were found on MRI without disease progression. All patients who did not have disease progression did not receive therapy during the posttransplantation period. HCT was accompanied by a significant improvement in quality of life, with statistically significant changes in most quality of life 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).8 (Another 35 patients had shorter follow-up, and the remainder were lost to follow-up.) Thirty (47%) of the 64 patients improved by at least 0.5 points on the EDSS score compared with baseline. Among the other patients, 29 (45%) were stable, and 5 (7%) experienced worsening disease.

In 2012, Mancardi et al reported on 74 consecutive patients with MS treated with autologous HCT following an intermediate-intensity conditioning regimen during in the period from 1996 to 2008.9 Thirty-six patients had secondary progressive disease and 25 had RRMS. Clinical and MRI outcomes were reported. The median follow-up was 48.3 months (range, 0.8-126 months). Two (2.7%) patients died from transplant-related causes. 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 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 2015 single-center case series by Burt et al reported on 151 patients, 123 with RRMS and 28 with secondary progressive MS. Patients were treated with nonmyeloablative HCT between 2003 and 2014. Six patients were not included in the outcomes 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). There were no treatment-related deaths. 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 pretransplant 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.

Several studies have focused on patients with aggressive MS. In 2011, Fassas et al reported on the long-term results of a single-center study that investigated the effect of HCT on the treatment of MS.11 After a median follow-up of 11 years (range, 2-15 years), the authors reported on the clinical and MRI outcomes of 35 patients with aggressive MS treated with HCT. The PFS rate at 15 years was 44% for patients with active central nervous system disease and 10% for those without (p=0.01); 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 nine of these patients, EDSS scores did not progress above baseline scores. Two patients died; one at 2 months, and the other at 2.5 years— both from transplant-related complications. Gadolinium-enhancing lesions were significantly reduced after mobilization but were maximally and persistently diminished post-HCT.

A 2014 multicenter case series by Burman et al reported on 48 patients with aggressive RRMS (defined as a disease with high relapse frequency, and who failed conventional therapy).12 Patients underwent autologous HCT. At the 5-year follow-up, relapse-free survival was 87%, and the EDSS score progression-free survival (defined as a deterioration in EDSS score of <0.5 points) was 77%. The rate of disease-free survival (no relapses, no new MRI lesions, no EDSS score progression) was 68%.

In 2016, Atkins et al published a phase 2 trial investigating the use of immunoablation and autologous HCT for the treatment of aggressive MS. Inclusion criteria were: poor prognosis, ongoing disease activity, and EDSS score between 3.0 and 6.0. Twenty-four patients enrolled, and all of them had a median follow-up of 6.7 years (range, 4-13 years). One patient died of transplant-related complications (hepatic necrosis following sepsis). The primary outcome (activity-free survival at 3 years after transplantation) was 70% (95% CI, 47% to 84%). 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 (HALT-MS) trial were published in 2017 by Nash et al. The trial evaluated 24 patients with MS who were treated with high-dose immunosuppression and autologous HCT. The median follow-up was 62 months (range, 12-72 months). Outcomes were PFS (91%; 90% CI, 75% to 97%), clinical relapse-free survival (87%; 90% CI, 69% to 95%), and MRI activity-free survival (86%; 90% CI, 68% to 95%). Patients experienced high rates of adverse events: 92% had grade 3, and 100% had grade 4 adverse events. The majority of adverse events occurred between the start of conditioning and day 29 in the trial.

Section Summary: Multiple Sclerosis
Evidence for the use of HCT in patients with MS consists of an RCT and many single-arm studies. The 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. Outcomes in the single-arm studies included PFS, relapse-free survival, disease activity-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 deaths.

SYSTEMIC SCLEROSIS/SCLERODERMA

Systematic Reviews
In 2015, van Laar et al conducted a systematic review of evidence on the use of HCT for treating poor-prognosis systemic sclerosis. They identified 3 RCTs comparing HCT with the standard of care (cyclophosphamide): a phase 2 trial and a completed phase 3 trial, both of which are described in the Randomized Controlled Trial section, plus a phase 3 trial (Scleroderma: Cyclophosphamide or Transplantation [SCOT]). SCOT has been completed and results presented at a 2016 American

College of Rheumatology conference. Results have not been published at the time of this update. Reviewers concluded that there is evidence HCT can result in significant improvements in skin thickness and functional outcomes. However, HCT is associated with serious toxicities that can be fatal. Additional trials are needed to assess how to reduce toxicity and to determine which patients with scleroderma would benefit most from HCT.

A review in 2011 by Milanetti et al summarized 8 phase 1 and 2 clinical studies using autologous HCT to treat systemic sclerosis. 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.

Randomized Controlled Trials
Results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published in 2014. ASTIS was a phase 3 RCT conducted in 10 countries at 29 centers with access to an EBMT-registered transplant facility. A total of 156 patients were recruited between March 2001 and October 2009. Patients were eligible if they were between 18 and 65 years of age; had diffuse cutaneous systemic sclerosis according to American Rheumatism Association criteria, with a maximum duration of 4 years; minimum modified RSS of 15 (range, 0-51; higher scores indicate more sever skin thickening); and involvement of heart, lungs, or kidneys. Patients were randomized to high-dose chemotherapy (intravenous cyclophosphamide 200 mL/kg over 4 consecutive days and intravenous rabbit antithymocyte-globulin 7.5 mg/kg total dose over 3 consecutive days) followed by CD34-positive selected autologous HCT support (n=79) or 12 monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m^2). Median follow-up was 5.8 years (interquartile range, 4.1-7.8 years). The primary end point was event-free survival, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney). Main secondary end points included treatment-related mortality, toxicity, and disease-related changes in modified RSS, organ function, body weight, and quality of life scores. The internal validity (risk of bias) of ASTIS was assessed according to the U.S. Preventive Services Task Force criteria for randomized trials. The trial was rated as poor quality according to this framework because of 2 fatal flaws: outcome assessment was not masked to patients or assessors, and 18 (24%) of 75 of 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 were allowed at the discretion of the investigators, adding further uncertainty to the results.

Of the 53 primary end point events recorded, 22 were in the HCT group (19 deaths, 3 irreversible organ failures; 8 patients died of treatment-related causes in the first year, 9 of disease progression, 1 of cerebrovascular disease, 1 of malignancy) and 31 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 event-free survival than the controls, with Kaplan-Meier curves for overall survival crossing at about 2

years after treatment, with the overall survival rate at that time estimated at 85%. According to the Kaplan-Meier curves, at 5 years, the overall survival rate was estimated at 66% in the control group and estimated at 80% in the HCT group (p value unknown). Time-varying hazard ratios (modeled with a treatment by time interaction) for event-free survival 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.

An open-label, randomized, controlled phase 2 trial (ASSIST; 2011) evaluated the safety and efficacy of autologous nonmyeloablative HCT compared with the standard of care (cyclophosphamide). Nineteen consecutively enrolled patients less than 60 years of age with diffuse systemic sclerosis, modified RSS greater than 14, and organ involvement or restricted skin involvement (modified RSS, <14) but coexistent pulmonary involvement were randomized 1:1 to HCT, intravenous cyclophosphamide 200 mg/kg, plus rabbit antithymocyte-globulin or to intravenous cyclophosphamide 1.0 g/m^2 once per month for 6 months. The primary outcome was an improvement at 12 months, which was defined as a decrease in modified RSS (<25% for those with initial modified RSS >14) or an increase in forced vital capacity of more than 10%. Patients in the control group with disease progression (>25% increase in modified RSS or decrease of >10% in forced vital capacity) despite treatment with cyclophosphamide could switch to HCT 12 months after enrollment. No deaths occurred in either group during follow-up. 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 (ie, disease progression without interval improvement), occurred in 8 of 9 controls but did not occur in any of the 10 patients treated by HCT (p<0.001). After long-term follow-up (mean, 2.6 years) of patients allocated to HCT, all but 2 patients had sustained improvement in modified RSS and forced vital capacity, with a 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 modified RSS from 27 (SD=15.5) to 15 (SD=7.4), an increase in forced vital capacity from 65% (20.6%) to 76% (26.5%), and an increase in total lung capacity from 81% (14.0%) to 88% (13.9%). Data for 11 patients, with a follow-up of to 2 years after HCT, suggested that the improvements in modified RSS (p<0.001) and forced vital capacity (p<0.03) persisted.

Nonrandomized Studies
Vonk et al (2008) reported on the long-term results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HCT from 1998 to 2004. 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 modified RSS, and a significant (ie, >25%) decrease (ie, 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 event-free survival 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%.

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. 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 overall survival 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. The main outcome variable was response to treatment (reduction of modified RSS by 25%) at 6 months. Secondary end points were transplant-related mortality and PFS. At 6 months, significant skin and lung function improvement assessed on the modified RSS was achieved in 78.3% of patients. Overall response rate was 91%, and some patients even improved after month 6. Three patients died between mobilization and conditioning treatment-two due to severe disease progression and one 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.

Section Summary: Systemic Sclerosis/Scleroderma
Evidence for the use of HCT in patients with systemic sclerosis/scleroderma consists of 3 RCTs and nonrandomized studies. Two RCTs (one with 19 patients, the other with 156 patients) have published results and reported statistically significant improvements in clinical outcomes (skin thickness, forced vital capacity). The larger trial (ASTIS) also reported improved overall survival. However, HCT can result in serious adverse events due to toxicity. The third RCT, completed and expected to be published soon, employed a different transplant regimen. Additional information on the best treatment regimen to reduce toxicity and long-term follow-up is still needed.

SYSTEMIC LUPUS ERYTHEMATOSUS
Burt et al (2006) published results on the largest single-center series using HCT for SLE in the United States. 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 treatment-related mortality rate of 4% (2/50). After a mean follow-up of 29 months (range, 6 months to 7.5 years), the 5-year overall survival rate was 84%, and the probability of disease-free survival was 50%. Several parameters of SLE activity improved, including renal function, Systemic Lupus Erythematosus 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. Overall survival 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 overall survival 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, one due to severe pneumonia and the other due to heart failure at 33 and 64 months after transplantation, respectively. The authors concluded that their 7-year follow-up results suggested that autologous HCT was beneficial for SLE patients.

Leng et al (2017) reported on 24 patients with severe SLE who received high-dose immunosuppressive therapy and HCT. 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 overall survival rate was 86%; 16 patients remained in remission, four were lost to follow-up, two had died, and one had active disease.

Section Summary: Systemic Lupus Erythematosus
Evidence for the use of autologous HCT to treat patients with SLE consists of several case series (total N=91 patients). A 4% treatment-related mortality rate was reported in 2 studies. High rates of remission were reported at 6 months, and at 2- to 10-year follow-ups. While HCT has shown beneficial effects on patients with SLE, further investigation of more patients is needed.

JUVENILE IDIOPATHIC OR RHEUMATOID ARTHRITIS
A 2008 review article by Saccardi et al on HCT for autoimmune diseases has summarized the experience with juvenile idiopathic arthritis and rheumatoid arthritis as follows.26 More than 50 patients with juvenile idiopathic arthritis have been reported to the EBMT Registry. The largest cohort study initially used a single conditioning regimen and, thereafter, a modified protocol. Overall drug-free remission rate was approximately 50%. Some late relapses have been reported, and only partial correction of growth impairment has been seen. The frequency of HCT for rheumatoid arthritis has decreased significantly since 2000, due to the introduction of new biologic therapies. Most patients who have undergone HCT have had persistence or relapse of disease activity within 6 months of transplant.

Section Summary: Juvenile Idiopathic or Rheumatoid Arthritis
Evidence for the use of HCT on patients with juvenile idiopathic arthritis consists of data from an EBMT Registry (N>50). Different conditioning regimens were used among the patients, 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.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY
Several review articles have summarized experience with HCT in the treatment of chronic inflammatory demyelinating polyneuropathy. 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.

Section Summary: Chronic Inflammatory Demyelinating Polyneuropathy
Evidence for the use of HCT to treat patients with chronic inflammatory demyelinating polyneuropathy consists of case reports. Additional investigations are needed due to the toxicity associated with this procedure.

TYPE 1 DIABETES

Systematic Reviews
In 2016, El-Badawy and El-Badri published a meta-analysis on the use of HCT to treat diabetes. The literature search, conducted through August 2015, identified 22 studies for inclusion. Fifteen of the studies (n=300 patients) involved patients with type 1 diabetes; 7 studies (n=224 patients) involved patients with type 2 diabetes. The quality of the selected studies was assessed using Cochrane criteria. The following items were evaluated to determine the risk of bias: attrition, confounding measurement, intervention, performance, selection, and conflict of interest. The mean follow-up in the studies ranged from 6 to 48 months (median, 12 months). Comparisons of C-peptide levels (C-peptide measures islet cell mass, and an increase after HCT indicates preservation of islet cells) and hemoglobin A1c levels after 12-month follow-up were calculated by type of diabetes (1 or 2) and source of stem cells (see Table 1). 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 1. Standard Mean Differences From Baseline in C-Peptide and HbA$_{1c}$ Levels in Patients With Diabetes Treated With HCT After 12 Months of Follow-Up

Diabetes Subgroups	No. of Studies	No. of Patients	SMD (95% CI) C-Peptide	No. of Studies	No. of Patients	SMD (95% CI) HbA$_{1c}$
Type 1						
UCB	4	56	1.07 (0.67 to 1.48)	4	61	0.05 (-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)
Type 2						
UCB	1	2	-0.55 (-4.23 to 3.13)	1	2	0.73 (-3.83 to 5.29)
UC-MSC	1	22	-0.61 (-1.21 to 0.00)	1	22	0.93 (0.30 to 1.55)
PD-MSC	1	10	-0.38 (-1.27 to 0.50)	1	10	1.50 (0.49 to 2.53)
BM-MNC	2	41	-1.29 (-1.77 to -0.81)	4	107	1.16 (0.85 to 1.46)
Total	5	75	-0.93 (-1.27 to -0.58)	7	141	1.14 (0.88 to 1.40)

Adapted from El-Badawy and El-Badri (2016).

BM-HSC: bone marrow hematopoietic stem cells; BM-MNC: bone marrow mononuclear stem cells; BM-MSC: bone marrow mesenchymal stem cells; CI: confidence interval; HbA1c: hemoglobin A1c; HCT: hematopoietic cell transplantation; IS-ADSc: insulin secreting-adipose derived stem cells; NA: not applicable; PD-MSC: placenta-derived mesenchymal stem cells; 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.

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

In 2015, Xiang et al 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. 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 2016 case series by Snarski et al reported on 24 patients with a diagnosis of type 1 diabetes who underwent autologous HCT. 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. 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.

In 2009, Couri et al reported on the results of a prospective case series evaluating autologous HCT in 23 patients with type 1 diabetes (age range, 13-31 years) diagnosed in the 6 weeks before transplant based on clinical findings including hyperglycemia and confirmed by measurement of serum levels of antiglutamic acid decarboxylase antibodies. At a mean follow-up of 29.8 months (range, 7-58 months) after autologous nonmyeloablative HCT, C-peptide levels increased significantly, and most patients achieved insulin independence with good glycemic control. Twenty patients without previous ketoacidosis and not receiving corticosteroids during the preparative regimen became insulin-free. Twelve patients maintained insulin independence for a mean of 31 months (range, 14-52 months), and 8 patients relapsed and resumed low-dose insulin. In the continuously insulin-independent group, hemoglobin A1c levels were less than 7.0%. There was no transplant-related mortality.

Section Summary: Type 1 Diabetes
Evidence for the use of HCT to treat diabetes consists of several case series and a meta-analysis of 22 studies. The meta-analysis revealed that HCT is more effective in patients with type 1 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; those factors are: heterogeneity in the stem-cell types, cell number infused, and infusion methods.
Adapted from El-Badawy and El-Badri (2016).
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SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS
American Academy of Neurology et al
A review of guidelines from the American Academy of Neurology and the American College of Rheumatology found no mention of stem cell transplantation for multiple sclerosis, lupus, rheumatoid arthritis, or juvenile idiopathic arthritis. In 2016, the Academy affirmed the statements in the Myasthenia Gravis Foundation of America's consensus guidelines for the management of

myasthenia gravis. The consensus guidelines did not discuss hematopoietic cell transplantation (HCT) as a therapeutic option.

American Society for Blood and Marrow Transplantation
In 2015, the American Society for Blood and Marrow Transplantation published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial setting. Table 2 lists guidelines for specific indications addressed in this evidence review.

Table 2. Recommendations for the Use of HCT to Treat Autoimmune Diseases

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

D: developmental; HCT: hematopoietic cell transplantation; N: not generally recommended; R: standard of care, rare indication.

European Group for Blood and Marrow Transplantation
In 2012, the European Group for Blood and Marrow Transplantation (EBMT) updated its guidelines on HCT for severe autoimmune diseases. EBMT recommended as follows: "HSCT [hematopoietic stem cell transplantation] should be considered as a therapeutic option at second line or beyond for patients with severe ADs [autoimmune diseases] progressing despite standard established and/or approved therapy" (level of evidence II). The following conditions should be met if HCT is chosen for treatment: referral to a center with JACIE (Joint Accreditation Committee of International Society for Cellular Therapy and EBMT) accreditation; when possible, HCT should be conducted within a phase 2 or 3 trial; if such a phase 2 or 3 trial is not available, then a multidisciplinary team should meet with patients to discuss HCT and non-HCT treatment options.

In 2015, EBMT issued additional guidelines on HCT for severe autoimmune diseases, focusing on immune monitoring and biobanking. To standardize clinical HCT protocols, EBMT developed guidelines for "good laboratory practice" in relation to procuring, processing, storing, and analyzing biologic specimens of patients with autoimmune diseases undergoing HCT. The guidance provides a table that specifies the type of biologic sample (eg, serum, biopsy, cerebrospinal fluid), sample tests, testing methods (eg, enzyme linked immunosorbent assay, fluorescent activated cell sorter), and timing of testing for the following autoimmune diseases: multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, Crohn disease, type 1 diabetes, and arthritis.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

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 3.

Table 3. 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 … 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study"
Autologous HCT
"Effective … 1989, [autologous HCT] is considered reasonable and necessary … for the following conditions and is covered under Medicare for patients with: 1. Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched; 2. Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response; 3. Recurrent or refractory neuroblastoma; or, 4. Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor."
"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: a) Acute leukemia not in remission; b) Chronic granulocytic leukemia; c) Solid tumors (other than neuroblastoma); d) Up to October 1, 2000, multiple myeloma; e) Tandem transplantation (multiple rounds of [autologous HCT]) for patients with multiple myeloma; f) Effective … 2000, non primary AL amyloidosis; and, g) 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."

HCT: hematopoietic cell transplantation.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02516124	Autologous Stem Cell Transplantation for Progressive Systemic Sclerosis: a Prospective Non-interventional Approach Across Europe (NISSC) for the Autoimmune Diseases Working Party of the EBMT	82	Jan 2018
NCT01445821	Randomized Study of Different Non-myeloablative Conditioning Regimens with Hematopoietic Stem Cell Support in Patients with Scleroderma (ASSIST-IIb)	160	Sep 2018
NCT00273364	Hematopoietic Stem Cell Therapy for Patients With Inflammatory Multiple Sclerosis Failing Alternate Approved Therapy: A Randomized Study	110	Dec 2018
NCT00278629	Non-myeloablative Autologous Hematopoietic Stem Cell Transplantation in Patients With Chronic Inflammatory Demyelinating Polyneuropathy: A Phase II Trial	80	Dec 2018
NCT02225795	A Pilot Study of Autologous Stem Cell Transplantation with Post-transplant Cyclophosphamide for Children and Young Adults with Refractory Crohn's Disease	15	Dec 2019
NCT02674217	Outpatient Hematopoietic Grafting in Patients with Multiple Sclerosis Employing Autologous Non-cryopreserved Peripheral Blood Stem Cells: a Feasibility Study	200	Dec 2019
NCT03113162	Evaluation of the Safety and Efficacy of Reduced-Intensity Immunoablation and Autologous Hematopoietic Stem Cell Transplantation (AHSCT) in Multiple Sclerosis	15	May 2020
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
Unpublished			
NCT00114530	A Randomized, Open-label, Phase II Multicenter Study of High-Dose Immunosuppressive Therapy Using Total Body Irradiation, Cyclophosphamide, ATGAM, and Autologous Stem Cell Transplantation with Auto-CD34+HPC versus Intravenous Pulse Cyclophosphamide for the Treatment of Severe Systemic Sclerosis	75	Apr 2016 (completed)

NCT: national clinical trial.

V. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

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