



Hematopoietic Cell Transplantation for Autoimmune Diseases

Effective: August 1, 2026

Next Review: April 2027

Last Review: June 2026

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Hematopoietic cell transplant has been proposed as a treatment for autoimmune diseases, including multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis/scleroderma.

MEDICAL POLICY CRITERIA

Notes: Clinical documentation to support criteria is required (See Required Documentation)

Medically Necessary

- I. Hematopoietic cell transplantation may be considered **medically necessary** as a treatment of systemic sclerosis/scleroderma if all of the following criteria are met (A. – H.):
 - A. Transplant is an autologous hematopoietic cell transplant; and
 - B. Individual is 18 to 60 years of age; and
 - C. Condition has been present less than or equal to 5 years; and

- D. Modified Rodnan Scale Scores greater than or equal to 15; and
- E. Internal organ involvement, as indicated by one or more of the following:
 - 1. Cardiac: abnormal electrocardiogram; or
 - 2. Pulmonary involvement, as indicated by one or more of the following:
 - a. Diffusing capacity of carbon monoxide (DLCo) <80% of predicted value; or
 - b. Decline of forced vital capacity (FVC) of >10% in last 12 months; or
 - c. Pulmonary fibrosis; or
 - d. Ground glass appearance on high resolution chest CT; or
 - 3. Renal: scleroderma-related renal disease
- F. History of < 6 months treatment with cyclophosphamide; and
- G. No active gastric antral vascular ectasia; and
- H. All of the following are met (1. – 7.):
 - 1. Left ventricular ejection fraction >50%
 - 2. Tricuspid annular plane systolic excursion >1.8 cm
 - 3. Pulmonary artery systolic pressure <40 mm Hg
 - 4. Mean pulmonary artery pressure <25 mm Hg
 - 5. DLCo >40% of predicted value
 - 6. FVC >45% of predicted value
 - 7. Creatinine clearance of >40 ml/min

Investigational

- II. Autologous and allogeneic hematopoietic cell transplantation is considered **investigational** as a treatment of systemic sclerosis/scleroderma when Criterion I. is not met.
- III. Autologous and allogeneic hematopoietic cell transplantation is considered **investigational** as a treatment of autoimmune diseases, including, but not limited to:
 - A. Autoimmune hepatitis and cryptogenic cirrhosis
 - B. Behçet's disease
 - C. Chronic inflammatory demyelinating polyneuropathy (CIDP)
 - D. Crohn's Disease
 - E. Diabetes mellitus, type I
 - F. GI autoimmune diseases including Crohn's disease, ulcerative colitis, and celiac disease
 - G. Immune cytopenias including but not limited to: autoimmune hemolytic anemia, Evans' s syndrome, immune thrombocytopenia, pure red cell or white cell aplasia, and thrombotic thrombocytopenia purpura

- H. Immune vasculitis
- I. Juvenile idiopathic arthritis
- J. Multiple sclerosis (MS)
- K. Neuromyelitis optica
- L. Relapsing polychondritis
- M. Rheumatoid arthritis (RA)
- N. Systemic lupus erythematosus (SLE)

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

REQUIRED DOCUMENTATION

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and physical/chart notes
- Diagnosis and indication for transplant
- Measures of organ involvement, as outlined in the Policy Criteria

CROSS REFERENCES

1. [Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant](#), Transplant, Policy No. 45.03
2. [Placental and Umbilical Cord Blood as a Source of Stem Cells](#), Transplant, Policy No. 45.16

BACKGROUND

AUTOIMMUNE DISEASES

Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, with some of the most common types being multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis/scleroderma.

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).

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, these drugs are not curative, and a proportion of patients will have severe, recalcitrant, or rapidly progressive disease. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT).

HCT in autoimmune disorders raises the question of whether ablating and “resetting” the immune system can alter the disease process and sustain remission, and possibly lead to

cure.^[1] Certain hematologic malignancies, aplastic anemia, and inborn errors of metabolism are treated with HCT.^[1] However, its usage in autoimmune diseases has only been performed in approximately 1,000 patients in the last decade.^[1]

The rationale for HCT for autoimmune disease is based on studies in experimental animal models, and on observations of remissions of autoimmune disease in patients who received HCT for hematologic malignancies.^[2]

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT, previously referred to in this policy as hematopoietic stem cell transplant [HSCT]) 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 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 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 six. 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 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.^[3] This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablative), as is often performed in autologous HCT for hematologic malignancies.^[3] However, there is currently no standard conditioning regimen for autoimmune diseases and both lymphoablative and myeloablative regimens are used.^[1] The efficacy of the different conditioning regimens has not been compared in clinical trials.^[1]

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.^[1]

ALLOGENEIC CELL TRANSPLANTATION FOR AUTOIMMUNE DISEASES

The experience of using allogeneic HCT for autoimmune diseases is currently limited,^[1] 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.^[1]

EVIDENCE SUMMARY

Ideally, for autologous and/or allogeneic hematopoietic cell transplant (HCT) to be considered as a treatment for autoimmune disease, comparative studies with long-term follow-up are necessary in order to determine the durability of any beneficial treatment effects, and to establish guidelines regarding the timing of hematopoietic cell transplant. In order to establish guidelines for conditioning regimens, clinical studies that compare these therapies are also needed.

VARIOUS DISEASES

A systematic review prepared by the BCBSA TEC Evidence-based Practice Center for the Agency for Healthcare Research and Quality (AHRQ) evaluated the use of HCT among pediatric patients (age 21 or younger) with various medical conditions (cancer, metabolic disease or autoimmune disease).^[4] Despite the lack of consistency in reported health outcomes and the rarity of randomized controlled trials, the review found that moderate-level evidence existed to support the association between single autologous HCT and “extended periods of drug-free clinical remission” among patients with newly diagnosed type 1 juvenile diabetes, and severe, refractory juvenile idiopathic arthritis, systemic lupus, systemic sclerosis, and Crohn’s disease. Nevertheless, the review concluded that “The overall body of evidence is insufficient to draw conclusions about the comparative benefits (e.g., increased overall survival) or harms (treatment-related mortality, secondary malignancies) of single autologous or allogeneic HCT versus conventional therapy or disease natural history in patients with newly diagnosed type 1 diabetes mellitus, or those with severe, refractory, poor prognosis autoimmune diseases, including: systemic lupus erythematosus, juvenile idiopathic arthritis, systemic sclerosis, malignant multiple sclerosis, Crohn’s disease, myasthenia gravis, overlap syndrome, diffuse cutaneous cutis, Evans syndrome, autoimmune hemolytic anemia, and autoimmune cytopenia.” The review recommended that additional controlled trials of adequate duration are required to evaluate the net benefit of HCT among pediatric patients with autoimmune disease.

A report from the British Society of Blood and Marrow Transplantation (BSBMT) data registry reported on long-term health outcomes of patients with one or more autoimmune diseases treated with autologous or allogeneic HCT from 1997 to 2009.^[5] Data for 69 patients were reported (representing less than 1% of the total number of patients treated with HCT in the United Kingdom in that time period). One and five-year rates of overall survival (OS) were estimated at 85% and 78%, respectively, for patients treated with autologous transplantation, and 87% and 65%, respectively, for patients treated with allogeneic transplantation. Younger age at transplantation and lack of a connective tissue disorder (such as systemic lupus erythematosus) were associated with improved outcomes. Nevertheless, the authors caution that these results “should be viewed in the context of translational and developmental phases of this approach [HSCT] to poor prognosis and refractory autoimmune disease.” They recommend the increased adoption of HSCT for individuals with autoimmune disease, but advocate that this take place in “prospective clinical studies in centres with a special interest.”

MULTIPLE SCLEROSIS

Systematic Reviews

Nabizadeh (2022) conducted a systematic review and meta-analysis on the use of autologous HCT in patients with MS.^[6] Fifty studies, including seven RCTs, with a total of 4831 patients

were included. The pooled estimated PFS was 73% (95% confidence interval [CI] 69% to 77%; I²= 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 other disease-modifying therapies when evaluating long-term outcome measures; the analysis considered an endpoint of all TRM at the end of a 5-year follow-up duration. Limitations of the meta-analysis include possible publication bias, minimal number of RCTs, lack of studies focusing on specific subtypes of MS, high heterogeneity between included studies, and unspecified duration of follow-up across studies.

Zhang (2020) performed a systematic review and meta-analysis of autologous HCT for multiple sclerosis and neuromyelitis optica spectrum disorder (NMOSD).^[7] A total of 27 studies met inclusion criteria, with 24 including MS (n=1,626) patients and three including NMOSD (n=31) patients. No evaluation of bias or quality was reported. The PFS for autologous HCT was 74% for MS and 76% for NMOSD. Subgroup analyses indicated that in MS patients, intermediate-, low-, and high-intensity regimens resulted in 73%, 85%, and 58% PFS, respectively. Computed TRM was 1% for MS and 9% for NMOSD.

A systematic review and meta-analysis by Ge (2019) evaluated the long-term safety and efficacy of autologous HCT for multiple sclerosis (MS).^[8] A total of 18 studies met inclusion criteria and included a total of 732 patients. Mean follow-up after HCT ranged from 19 months to 6.7 years and the number of patients ranged from 14 to 145. Four studies used high-intensity conditioning regimens. The progression-free survival (PFS) was 75% (95% confidence interval [CI] 0.69 to 0.81). The estimated treatment-related mortality was 1.34% (95% CI, 0.39 to 2.30), and the overall mortality was 3.58%. Subgroup analyses showed that factors associated with higher PFS were low- and intermediate-intensity regimens and relapsing remitting MS. Treatment-related mortality was 3.13% in patients receiving high-intensity conditioning.

Sormani (2017) conducted a systematic review and meta-analysis on the use of autologous HCT for the treatment of patients with severe treatment-refractory MS.^[9] The studies differed in types and intensities of conditioning regimens used before HCT: low (n=2), intermediate (n=7), high (n=4), and mixed (n=2). Quality assessment of included studies was not discussed. Rate of progression at two and five years were calculated, as well as treatment-related mortality (defined as number of deaths within 100 days of transplant/number of transplants) and overall mortality (defined as total number deaths/number of patient-years). A total of 764 patients were included in the meta-analysis. The pooled proportion of patients with no evidence of disease activity at two years was 83% (range 70 to 92%) and at five years was 67% (range 59 to 70%). Pooled treatment-related mortality was 2.1% (95% CI 1.3 to 3.4) and overall mortality was 1.0% (95% CI 0.7 to 1.5)

A 2011 systematic review by Reston evaluated the safety and efficacy of autologous HCT in patients with progressive MS refractory to conventional medical treatment.^[10] Eight small case series which monitored progression-free survival (PFS) with a median follow-up of at least two years were included. An additional six studies were included for a summary of mortality and morbidity. There was substantial heterogeneity across the eight case series. The majority of patients (77%) had secondary progressive MS, although studies also included those with primary progressive, progressive-relapsing, and relapse-remitting disease. Numbers of patients across studies ranged between 14 and 26. The studies differed in the types and

intensities of conditioning regimens used prior to HCT, with five studies using an intermediate-intensity regimen, while the other three used high-intensity regimens. All of the studies were rated of moderate quality. The estimated rate of long-term PFS of patients receiving 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 on adverse events, 13 were case series; from these, a total of seven treatment-related deaths were recorded; six non-treatment-related deaths occurred, five associated with disease progression.

A meta-analysis by Li (2016) found significant heterogeneity in 12 studies of HCT for MS.^[11] At 12-months follow-up, there was a statistically significant decrease in the Expanded Disability Status Scale (EDSS) scores of patients compared to baseline (-0.62; 95% CI -0.14 to -1.12). The authors concluded that while there was evidence that suggested a clinical benefit to this treatment, studies were limited by small sample sizes, and randomized controlled trials were needed.

Randomized Controlled Trials

Burt (2019) conducted a randomized controlled trial (RCT) comparing nonmyeloablative HCT with disease modifying therapy.^[12] The study included 110 patients with relapse-remitting MS, with 98 patients evaluated at one year. Inclusion criteria were a minimum of two relapses while receiving disease modifying therapy in the last year or one relapse and at a separate time in the past 12 months the presence of MRI gadolinium-enhancing lesion(s), and an EDSS (score range, 0 to 10, where 10=worst neurologic disability) score of 2.0 to 6.0. Patients were randomized into two groups, those receiving disease modifying therapy and those receiving HCT. Patients could crossover from disease modifying therapy to HCT at one year if they experienced progression of disability. The primary outcome was disease progression, which was defined as an EDSS score of increase after at least one year of 1.0 point or more on two evaluations six months apart. Disease progression occurred in three patients who received HCT and 34 patients in the group receiving disease modifying therapy. Other measures reported included changes in EDSS scores, which improved from 3.38 to 2.36 in the HCT group and worsened from 3.31 to 3.98 in the disease modifying therapy group.

Nonrandomized Studies

Genchi (2023) published the results of STEMS, a prospective, therapeutic exploratory, non-randomized, open-label, single-dose-finding phase 1 clinical trial evaluating the feasibility, safety and tolerability of intrathecally transplanted human fetal neural precursor cells (hfNPCs) in 12 patients with PMS (with evidence of disease progression, Expanded Disability Status Scale ≥ 6.5 , age 18-55 years, disease duration 2-20 years, without any alternative approved therapy).^[13] The authors reported the safety primary outcome was reached, with no severe adverse reactions related to hfNPCs at 2-year follow-up, clearly demonstrating that hfNPC therapy in PMS is feasible, safe and tolerable. Though of value to future clinical trials, these results need a lot more validation.

Burt (2021) performed a retrospective cohort study of 414 patients with relapsing-remitting multiple sclerosis (RRMS) and 93 patients with newly diagnosed secondary-progressive MS treated with HCT at a single center in the US between 2003 and 2019.^[14] Median follow-up was three years. Treatment-related mortality was 0.19% (one patient), PFS for RRMS was 95%, and for secondary-progressive multiple sclerosis was 66%. Additionally, relapse-free

survival at five years for patients with RRMS and secondary-progressive MS was 80.1% and 98.1%, respectively.

Boffa (2021) analyzed long-term outcomes following transplant in a cohort of MS patients.^[15] A total of 210 MS patients, of whom 122 were relapse-remitting, who had received an autologous HCT were included. The mean follow-up was 5.2 years. Disability worsening-free survival at five and ten years was 85.5% and 71.3%, respectively, in relapse-remitting patients and 71.0% and 57.2%, respectively, in patients with progressive MS. EDSS reduced significantly following transplant, with a mean EDSS change per year of -0.09 (95% CI -0.15 to -0.04%; $p=0.001$).

Kvistad (2019) performed a retrospective cohort study of 30 patients in Norway with relapsing/remitting MS treated with HCT between 2015 and 2018.^[16] At a two-year follow-up, two patients (7%) had a progression of 1.0 point of the EDSS score. Additionally, 13 (43%) patients experienced sustained improvement in EDSS score of 1 or more, and 25 patients (83%) experienced no evidence of disease activity. There was no treatment-related mortality reported.

Burman (2017) conducted a registry-based study of autologous HCT for pediatric MS patients.^[17] Using data from the European Society for Blood and Marrow Transplantation registry, 21 patients were identified, with a median follow-up of 2.8 years. Of these, 16 (76%) had improved EDSS scores and two patients had a disease relapse. There were also two incidences of severe transplant-related toxicity, but neither were fatal.

Burt (2009) transplanted 21 patients with relapsing-remitting MS with ongoing relapses during treatment with interferon.^[18] The conditioning regimen was nonmyeloablative. With a median follow-up of 37 months, 16 patients remained free of relapse, whereas 17 of the 21 patients had a one-point or greater improvement in their EDSS scores.

Guimaraes (2010) studied quality of life in 34 MS patients. At one year post transplantation, 27 (79%) patients showed stabilization or neurological improvement and statistically significant improvement in all domains of health-related quality of life.^[19]

The European Society for Blood and Marrow Transplantation (EBMT) autoimmune diseases working party database published results on a retrospective study of 178 patients with MS who underwent autologous HCT.^[20] After median follow-up of 42 months, the disease remained stable or improved in 63% of the group. In sub-group analysis, autologous HCT was found to be associated with significantly better progression-free survival in younger patients (i.e., younger than 40 years of age) with severe, progressive MS diagnosis compared to those older than 40 years. However, the authors caution that the role of autologous SCT in the treatment of refractory MS needs to be established through prospective randomized, controlled trials. Several editorials concur with the view that the role of autologous HCT is not established in MS or other autoimmune diseases.^[21-23]

Fassas (2011) reported the long-term results of a Phase I/II study conducted in a single center that investigated the effect of HCT in the treatment of MS.^[24] The authors reported on the clinical and MRI outcomes of 35 patients with aggressive MS treated with HCT after a median follow-up period of 11 (range 2 to 15) years. Disease PFS at 15 years was 44% for patients with active central nervous system (CNS) disease and 10% for those without ($p=0.01$); median time to progression was 11 years (95% CI 0 to 22) and two years (0 to 6). Improvements by 0.5 to 5.5 (median 1) Expanded Disability Status Scale (EDSS) points were observed in 16 cases lasting for a median of two years. In nine of these patients, EDSS scores did not

progress above baseline scores. Two patients died, at two months and 2.5 years, from transplant-related complications. Gadolinium-enhancing lesions were significantly reduced after mobilization but were maximally and persistently diminished post-HCT. The authors concluded that HCT should be reserved for aggressive cases of MS, still in the inflammatory phase of the disease, and for the malignant form, in which it can be life-saving, and that HCT can result in PFS rates of 25% and can have an impressive and sustained effect in suppressing disease activity on MRI.

Shevchenko (2012) reported the results of a prospective Phase II open-label single-center study which analyzed the safety and efficacy of autologous HCT with reduced-intensity conditioning regimen in 95 patients with different types of MS.^[25] The patients underwent early, conventional, and salvage/late transplantation. The efficacy was evaluated based on clinical and quality-of-life outcomes. No transplantation-related deaths were observed. All of the patients, except one, responded to the treatment. At long-term follow-up (mean 46 months), the overall clinical response in terms of disease improvement or stabilization was 80%. The estimated PFS at five years was 92% in the group after early transplant versus 73% in the group after conventional/salvage transplant ($p=0.01$). No active, new, or enlarging lesions in MRI were registered in patients without disease progression. All patients who did not have disease progression were off therapy throughout the post-transplantation period. HCT was accompanied by a significant improvement in quality of life with statistically significant changes in the majority of quality-of-life parameters ($p<0.05$). A 2015 publication reported on 64 patients participating in this study who had at least 36 months follow-up. Thirty of the 64 patients (47%) improved at least 0.5 points on the EDSS scale compared to baseline.^[26] Among the other patients, 29 (45%) were stable and five (7%) experienced worsening disease.

In a small, phase II, RCT ($n=21$), Mancardi (2015) reported results of the effect of HCT compared with mitoxantrone on disease variables in patients with severe MS.^[27] Patients were randomized to either receive intense immunosuppression with a combination of drug therapy, followed by HCT or mitoxantrone (20 mg) every six months. The primary outcome measure was the total number of new T2 lesions during four years of follow-up. Results demonstrated that HCT reduced the total number of new T2 lesions compared with mitoxantrone (rate ratio, 0.21; $P=0.00016$). However, rates of disability did not change in either group. Hence, the clinical significance of the reduction in T2 lesions is unclear.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Leone (2018) conducted a systematic review of clinical and laboratory studies using autologous HCT for patients with systemic lupus erythematosus (SLE).^[28] The literature search, conducted through 2014, identified 25 studies ($n=279$ patients): two 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 five studies reporting deaths, resulting in an overall mortality of 8.3% in a mean followup of 36 months.

Burt (2018) reported on 30 patients with refractory, chronic, corticosteroid dependent SLE who underwent autologous HCT.^[29] Outcomes were measured at six months and yearly through five years. Disease remission was achieved by 24 patients. The SLE Disease Activity Index and quality of life (SF-36) improved significantly at each followup compared with baseline. No treatment-related mortality was reported. Five grade 4 and 60 grade 3 adverse events were reported.

Cao (2017) reported on 22 patients with SLE who underwent autologous peripheral blood HCT.^[30] At five-year followup, PFS was 68% and overall survival was 95%. At last followup, 10 patients had relapsed. Adverse events included infections, secondary autoimmunity, lymphoma, and malignancy. The authors noted a difficulty in distinguishing between conditions caused by relapse or by the transplantation.

A systematic review by Leone (2017) evaluated the use of HCT in SLE and antiphospholipid syndrome (APS).^[28] The authors found 25 studies that met inclusion criteria, with a total of 279 SLE patients, 54 of whom also had APS. While most of these studies reported improvements after HCT, one study found no benefit to transplant compared with immunosuppression alone. There were 32 out of 44 patients with APS were able to discontinue anticoagulation following transplantation. However, the authors noted a relatively high rate of adverse events, including 86 infections (30.8%), with three that were fatal.

Burt (2006) published the results of a prospective case series on the use of autologous HCT as salvage treatment in 50 patients (mean age 30; 43 women, seven men) with SLE refractory to standard care.^[31] Patients underwent autologous SCT following a lymphoablative conditioning regimen and primary outcomes consisted of overall survival (OS) and disease-free survival. Treatment-related mortality was 4% (2/50) and after a mean follow-up of 29 months (range, six months to 7.5 years), estimated five-year survival was 84%, and the estimated probability of disease-free survival at five years was 50%. The investigators suggest these results justify a randomized trial comparing immunosuppression plus autologous HCT versus continued standard of care. An editorial by Petri and Brodsky that accompanied this article concurred that randomized clinical trials are needed to determine whether this treatment approach improves outcomes when compared with conventional therapies.^[32]

A report from the EBMT Autoimmune Disease Working Party on the variables associated with development of a secondary autoimmune disease following autologous HCT in a group of 347 patients (with various primary autoimmune diseases) identified SLE as a risk factor for this complication (using multivariate analysis).^[33] This finding points to the need for prospective, randomized, controlled trials to identify factors pre-disposing patients, specifically those with SLE, to development of a secondary autoimmune disease.

SYSTEMIC SCLEROSIS/SCLERODERMA

Systematic Reviews

Higashitani (2023) conducted a systematic review and meta-analysis of survival outcomes of HCT in patients with systemic sclerosis.^[34] There were 22 studies included (three 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 (2022) conducted a systematic review of autologous HCT for the treatment of systemic sclerosis.^[35] There were 3 RCTs (N=125) included (described below) with three 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.

Shouval (2018) conducted a meta-analysis of four studies (three RCTs, all described below in detail) and one retrospective comparative study) on the use of autologous HCT compared with cyclophosphamide alone for the treatment of systemic sclerosis.^[36] Quality assessment of the three RCTs found that two of the RCTs had low risk in the randomization methods and outcome reporting, one RCT was unclear in randomization methods, and all three were high risk since blinding of patients and outcome assessors was not conducted. Meta-analyses of the RCTs showed that all-cause mortality favored HCT (risk ratio 0.6; 95% CI 0.4 to 0.9) and treatment-related mortality favored cyclophosphamide alone (risk ratio 10.8; 95% CI 1.4 to 85.7).

Host (2017) conducted a systematic review of autologous HCT for the treatment of systemic sclerosis.^[37] The literature search, conducted through March 2016, identified nine studies (two RCTs and seven observational studies) for inclusion. The RCTs reported improvements in progression- and event-free survival and all studies reported improvements in modified Rodnan Skin Score. However, treatment-related mortality rates ranged from 0% to 23%, with higher rates found with higher doses of cyclophosphamide or myeloablative conditioning regimens. No pooled analysis was conducted.

Randomized Controlled Trials

Sullivan (2018) conducted an RCT comparing autologous HCT with cyclophosphamide for the treatment of scleroderma.^[38] Adult patients with scleroderma with maximum duration five years, active interstitial lung disease and scleroderma-related renal disease were eligible. The trial was originally designed for 226 patients, but due to low accrual, a total of 75 patients participated. Patients were randomized to receive total body irradiation (800 cGy), cyclophosphamide (120 mg/kg), equine antithymocyte globulin (90 mg/kg), and autologous HCT (n=36) or 12 monthly treatments with intravenous pulsed cyclophosphamide (n=39). Of the 36 patients randomized to receive HCT, 27 completed the trial per protocol (three died and six 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 modified RSS. There were more percent pairwise comparisons favoring HCT over cyclophosphamide alone at 4 and 4.5 years followup. The following disease progression events were significantly higher among patients receiving cyclophosphamide alone: initiating disease-modifying antirheumatic drugs, congestive heart failure leading to treatment, and pulmonary arterial hypertension. The following disease progression events were not significantly different among the two treatment groups: arrhythmia, pericardial effusion, renal crisis, and myositis. Death or respiratory, renal, or cardiac failure occurred in 28% and 51% of HCT and cyclophosphamide patients, respectively, at four years (p=0.06). Death from any cause occurred in 17% and 11% of HCT and cyclophosphamide patients, respectively, at four and a half years (p=0.28).

The results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS)

trial (ISRCTN54371254) were published in June 2014.^[39] ASTIS was a Phase III 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. Individual 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 maximum duration of four years; minimum modified Rodnan skin score (mRSS) of 15 (range, 0 to 51 with higher scores indicating more severe skin thickening); and involvement of heart, lungs, or kidneys. Patients were randomly allocated to receive high-dose chemotherapy (intravenous cyclophosphamide 200 mg/kg over four consecutive days and intravenous rabbit antithymocyte globulin 7.5 mg/kg total dose over three consecutive days) followed by CD34+ selected autologous HCT support (n=79) or 12 monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m²). Median follow-up was 5.8 years (interquartile range, 4.1 to 7.8 years). The primary end point was event-free survival, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney). Main secondary end points included treatment-related mortality, toxicity, and disease-related changes in mRSS, organ function, body weight, and quality-of-life scores.

A total of 53 primary end point events were recorded: 22 in the HCT group (19 deaths and three irreversible organ failures; eight patients died of treatment-related causes in the first year, nine of disease progression, one of cerebrovascular disease, one of malignancy) and 31 in the control group (23 deaths and eight irreversible organ failures [seven of whom died later]; 19 patients died of disease progression, four of cardiovascular disease, five of malignancy, two of other causes). The data show patients treated with HCT experienced more events in the first year but appeared to have better long-term event-free survival than the controls, as the Kaplan-Meier curves for overall survival (OS) cross at about two years after treatment with OS at that time estimated at 85%. According to data from the Kaplan-Meier curves, at five years, OS was an estimated 66% in the control group and about 80% the HCT group (p value unknown). Time-varying hazard ratios (modeled with treatment x time interaction) for event-free survival were 0.35 (95% CI, 0.15 to 0.74) at two years and 0.34 (95% CI, 0.16 to 0.74) at four years, supporting a benefit of HCT versus pulsed cyclophosphamide. Severe or life-threatening grade 3 or 4 adverse events were reported in 51 (63%) of the HCT group compared with 30 (37% by intention-to-treat, p=0.002).

The internal validity (risk of bias) of ASTIS was assessed according to the United States Preventive Services Task Force (USPSTF) criteria for randomized trials. The study was rated as “poor” quality according to this framework because it has two major flaws: outcome assessment was not masked to patients or assessors, and 18 of 75 (24%) of the control group discontinued intervention because of death, major organ failure, adverse events, or non-adherence. Furthermore, the study allowed crossover after the second year, but whether any patients did so and were analyzed as such is not mentioned. Finally, the authors report 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.

An open-label, randomized, controlled phase II trial (ASSIST) assessed the safety and efficacy of autologous non-myeloablative HCT compared with the standard of care for systemic sclerosis.^[40] A small group of consecutively enrolled patients (n=19), all younger than 60 years of age, with diffuse systemic sclerosis were randomly allocated by use of a computer-generated sequence to receive HCT, 200 mg/kg intravenous cyclophosphamide, and rabbit antithymocyte globulin or to 1.0 g/m² intravenous cyclophosphamide once per month for six

months. The primary outcome was improvement at 12 months' follow-up, defined as a decrease in mRSS (<25% for those with initial mRSS >14) or an increase in forced vital capacity by more than 10%. Patients in the control group with disease progression (>25% increase in mRSS or decrease of >10% in forced vital capacity) despite treatment with cyclophosphamide could switch to HCT 12 months after enrollment. No deaths occurred in either group during follow-up. Patients allocated to HCT (n=10) improved at or before 12 months' follow-up, compared with none of the nine allocated to cyclophosphamide (p=0.00001). Treatment failure (i.e., disease progression without interval improvement), occurred in eight of nine controls compared with none of the 10 patients treated by HCT (p=0.0001). After long-term follow-up (mean 2.6 years) of patients who were allocated to HCT, all but two patients had sustained improvement in mRSS and forced vital capacity, with a longest follow-up of 60 months. Seven patients allocated to receive cyclophosphamide switched treatment groups at a mean of 14 months after enrollment and underwent HCT without complication, and all improved after HCT. Four of these patients followed for at least one year had a mean decrease in mRSS points from 27 (standard deviation [SD] 15.5) to 15 (SD 7.4), an increase in forced vital capacity from 65% (SD 20.6) to 76% (SD 26.5) and an increase in total lung capacity from 81% (SD 14.0) to 88% (SD 13.9%). Data for 11 patients with follow-up to two years after HCT suggested that the improvements in mRSS (p<0.0001) and forced vital capacity (p<0.03) persisted.

Nonrandomized Studies

Several nonrandomized studies evaluate stem cell transplantation as summarized below. However, lack of a comparison group limits the ability to identify the treatment effect experienced by these groups of patients over and beyond that experienced by patients undergoing standard care for systemic sclerosis.

Henrique-Neto (2021) reported longitudinal retrospective data from 70 adult systemic sclerosis patients who underwent HCT at a single Brazilian center.^[41] Median age was 35.9 years. Overall survival and progression-free survival were 81% and 70.5%, respectively, at eight-years post-transplant. Improvements in mRSS (from a baseline value of 24, range 8 to 51) were reported at all timepoints between six months and five years (baseline vs. six months, p=0.007; baseline vs. 12 months, p=0.0006; baseline vs. 24, 36, 48 and 60 months, p<0.0001). Cause of death was transplant-related toxicity in three patients, disease reactivation in nine patients, and thrombotic thrombocytopenic purpura in one patient.

Costa-Pereira (2020) evaluated the effect of autologous HCT on functional status of systemic sclerosis patients.^[42] A total of 27 systemic sclerosis patients were assessed at baseline and six and 12 months following transplant. Statistically significant improvements were reported for six- and 12-month outcomes vs. baseline for mRSS (p<0.01 and p<0.01), mouth opening (p=0.02 and p<0.01), hand function (DASH, p<0.01 and p<0.01; Cochin hand function scale, p<0.01 and p<0.01; strength, p<0.01 and p<0.01), physical capacity (six-minute walk test, p=0.02 and p=0.03) and the physical component score of the SF-36 questionnaire (p<0.01 and p<0.01). Physical capacity and quality of life were significantly correlated (R=0.62; p<0.01), as were skin involvement and wrist ROM measures (dominant hand, R=-0.65, p<0.01; non-dominant hand, R=-0.59; p<0.01).

van Bijnen (2020) performed a retrospective cohort study of 92 patients in the Netherlands with systemic sclerosis treated with HCT between 1998 and 2017.^[43] 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 five years of follow up, median values decreased for modified RSS from 26 to 6 and increased for FVC from 84% to 94%. Disease progression occurred in 22 (24%) patients. Twenty patients died, and 10 deaths were classified as treatment-related mortality.

Henes (2020) reported results of a prospective non-interventional study of autologous stem cell transplantation for progressive systemic sclerosis from the EBMT Autoimmune Disease Working Party.^[44] The primary endpoint was progression-free survival and secondary endpoints were overall survival, non-relapse mortality, response, and incidence of progression. A total of 80 patients were enrolled. Median follow-up was 24 months. Two-year progression-free survival was 81.8%. Two-year outcomes for overall survival, response, and incidence of progression were 90%, 88.7%, and 11.9%, respectively.

Nakamura (2018) evaluated HCT for systemic sclerosis in 14 patients diagnosed within three years prior to enrolling.^[45] Median follow-up was 137 months. At 10 years, overall survival was 93% and event-free survival was 40%. Additional immunosuppressive treatments were required in 43% of patients and HCT-related adverse events occurred in 43% of patients as well. One patient died of severe cardiomyopathy.

Henes (2012) reported on their experience with autologous HCT for systemic sclerosis in 26 consecutive patients scheduled for HCT between 1997 and 2009.^[46] The major outcome variable was the response to treatment (reduction of mRSS by 25%) at six months. Secondary endpoints were transplant-related mortality and PFS. At six months, significant skin and lung function improvement of the mRSS was achieved in 78.3% of patients. The overall response rate was 91%, as some patients improved after month six. Three patients died between mobilization and conditioning treatment, two due to severe disease progression and one whose death was considered treatment-related. Seven patients experienced a relapse during the 4.4 years of follow up. PFS was 74%. Four patients died during follow-up, and the most frequent causes of death were pulmonary and cardiac complications of systemic sclerosis. The authors concluded that autologous HCT resulted in significant improvement in most patients with systemic sclerosis.

JUVENILE AND RHEUMATOID ARTHRITIS

Muthu (2021) performed a systematic review of HCT for the treatment of rheumatoid arthritis.^[47] Of the 17 studies that met inclusion criteria, one was a randomized controlled trial, 11 were prospective and five were retrospective nonrandomized studies. Fourteen evaluated autologous HCT and three evaluated allogeneic HCT. A total of 233 patients were included, aged 18 to 65. There was significant heterogeneity among studies in the scales used for the assessment of the functional improvement and in the follow-up timeframe. There was a significantly improvement in the clinical grades of ACR criteria following HCT ($Z = 11.309$, $p < 0.001$). One death due to sepsis and two transplant-related deaths were reported. Major complications were reported in some studies, but they were not found to be a significant effect of treatment ($p = 0.983$).

Silva (2018) reported on 16 patients with juvenile arthritis refractory to standard therapy or who had failed autologous HCT, who underwent allogeneic HCT.^[48] Patients experienced significant improvements in arthritis and quality of life, with 11 children achieving drug-free remission at last followup. At median followup of 29 months, one patient died of probable sepsis following an elective surgery and one died of invasive fungal infection, for a treatment-related mortality rate of 12.5%.

A review article by Saccardi (2008) summarized the experience thus far with juvenile idiopathic and rheumatoid arthritis.^[49] More than 50 patients with juvenile idiopathic arthritis have been reported to the EBMT Registry. The largest cohort study initially used one 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. A new retrospective analysis is ongoing on behalf of the Autoimmune Diseases, Pediatric and Inborn Error EBMT Working Parties. 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 six months of transplant.

TYPE 1 DIABETES

Systematic Reviews

Sun (2020) published a meta-analysis on the use of HCT to treat type 1 diabetes using data from RCTs published to March 2019.^[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. Most domains of bias in the RCTs were rated as low or unclear risk. The meta-analysis included a total of 151 patients. Results of the meta-analysis found that, compared with insulin therapy, HCT therapy significantly reduced HbA1c levels, increased fasting C-peptide levels (C-peptide measures islet cell mass, and an increase after HCT indicates preservation of islet cells), and reduced insulin dosages at six 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.

Gan (2018) published a meta-analysis of the efficacy of stem cell transplantation in patients with type 1 diabetes.^[51] The literature search, conducted through January 2018 identified 22 studies that met inclusion criteria. Among these were nine RCTs with a control group and were double blinded. Eight of the nine were considered to be high quality. Studies were rated for quality using the Jadad scale. A pooled analysis was conducted using a random-effects model and the Begg's funnel plot. Additional subgroup analyses were performed. There was no evidence of significant publication bias. A meta-analysis of the RCTs indicated that HCT treatment increased C-peptide levels and reduced the glycated hemoglobin level compared with the control group. Two RCTs reported fasting plasma glucose at the 12-month follow-up. The pooled effect indicated a reduction in the HCT group ($p=0.004$) but not in the control group ($p=0.323$).

El-Badawy and El-Badri (2016) published a meta-analysis on the use of HCT to treat diabetes.^[52] 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; seven 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.; 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). 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. 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.

Nonrandomized studies

Several nonrandomized studies were identified evaluating autologous HCT in patients with new-onset type 1 diabetes. In the series, although a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high.

Gan (2018) evaluated the safety and clinical efficacy of autologous HCT in adolescent patients with newly-diagnosed type 1 diabetes.^[51] Of the 40 patients included, 20 received HCT and 20 were treated with insulin injections only. Fourteen of the HCT-treated patients and one insulin-treated patient were insulin-independent for 1.5 to 48 months. Of the 14 insulin-independent HCT patients, 11 relapsed (median time of 19.5 months). At the four-year follow-up, the daily insulin dosages were 0.49 IU/kg/day in the HCT and 0.79 IU/kg/day in the insulin-only group.

Walicka (2018) assessed metabolic control in patients with newly diagnosed type 1 diabetes mellitus following HCT treatment.^[53] The study included a total of 23 patients who received HCT and eight control patients. At six months post-transplantation, 22 of 23 transplant patients were insulin-free. At six years post-transplantation, only one transplant patient was insulin-free. Fasting plasma glucose was significantly higher in the control group than the transplanted patients at 36 months following transplant, but good glycemic control was reported throughout the observation period.

Cantu-Rodriguez (2016) published a study of 16 patients with type 1 diabetes who received a less toxic conditioning regimen and transplantation.^[54] The outpatient procedures were completed without severe complications. At the six-month follow-up, three (19%) were nonresponders, six (37%) partially independent from insulin, and seven (44%) were completely independent of insulin. Hemoglobin A1c levels decreased by a mean of -2.3% in the insulin-independent group.

In 2015, Xiang published data on 128 patients ages 12 to 35 years who had been diagnosed with type 1 diabetes no more than six weeks before study enrollment.^[55] After a mean follow-up of 28.5 months (range, 15 to 38 months), 71 patients (55%) were considered to be insulin-free. These patients had a mean remission period of 14.2 months (SD=6.1 months). The other 57 patients (45%) were insulin-dependent. The latter group includes 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 (one patient each); there was no transplant-related mortality. In multiple logistic regression analysis, factors independently associated with becoming insulin-free after autologous HCT were younger age at onset of diabetes, lower tumor necrosis factor α , and higher fasting C peptide.

A case series by Snarski (2015) reported on 24 patients with a diagnosis of type 1 diabetes within six weeks of enrollment who underwent autologous HCT.^[56] Patients had a mean age of 26.5 years (range, 18 to 34 years). After treatment, 20 of 23 patients (87%) went into diabetes remission, defined as being insulin-free with normoglycemia for at least 9.5 months. Median time of remission was 31 months (range, 9.5 to 80 months). Mean insulin doses remained

significantly lower than baseline doses at two and three years, but the insulin doses returned to pre-HCT levels at years four and five. Among patients (n=20) remaining in follow-up at the time of data analysis for publication, four (20%) remained insulin-free. Adverse events include neutropenic fever in 12 patients (50%). There were four cases of sepsis, including a fatal case of *Pseudomonas aeruginosa* sepsis. There was also one case of pulmonary emphysema after insertion of a central venous catheter.

Couri (2009) reported the results of a prospective Phase I/II study of autologous HCT in 23 patients with type 1 diabetes (age range, 13 to 31 years) diagnosed in the previous six weeks by clinical findings with hyperglycemia.^[57] After a mean follow-up of just over two years (29.8 months; range, 7 to 58 months) post-transplantation, the majority of patients achieved insulin independence with good glycemic control. There was no transplant-related mortality. Nevertheless, interpretation of these results is limited by lack of long-term follow-up of primary health outcomes (morbidity and mortality related to diabetes). Additionally, lack of a comparison group limits the possibility of ruling out chance as an explanatory factor.

CROHN DISEASE

A Cochrane systematic review of RCTs was published by El-Nakeep in 2022 on the use of stem cell transplantation (SCT) for the induction of remission in medically refractory Crohn's disease.^[58] Eighteen studies, including seven RCTs, met the selection criteria. Only three studies used blinding, and of these, one stated that blinding was inefficient. The evidence was concluded to be uncertain about the effect of SCT on achieving clinical remission compared to control/placebo (risk ratio (RR) 1.88, 95% CI 0.80 to 4.41; three studies). The evidence was concluded to be very uncertain about the effect of SCT on achieving Crohn's Disease Activity Index (CDAI) <150 at 24 weeks compared to control (RR1.02 95% CI 0.67 to 1.56; four studies), about the effect of SCT to cause no difference in the number of total adverse events as compared to the control/placebo (RR 0.99, 95% CI 0.88 to 1.13; four studies), and about the effect of SCT to decrease the withdrawal due to adverse events as compared to the control/placebo (RR 0.78, 95% CI 0.32 to 1.89; 3 studies). However, low-certainty evidence indicates that SCT is likely to increase the number of serious adverse events as compared to the control/placebo (RR 1.22, 95% CI 0.88 to 1.67; seven studies).

Brierley (2018) published a review of patients in the European Society for Blood and Marrow Transplantation registry undergoing autologous HCT for Crohn disease (n=82) who had failed a median of six lines of drug therapy.^[59] At median followup 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 followup, 73% resumed medical therapy for Crohn disease.

Hawkey (2015) has conducted the only RCT (ASTIC trial) evaluating the effect of HCT on Crohn disease.^[60] Patients were randomized to receive either immunoablation and HCT (n=23) or control (HCT deferred for one 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 three months; and no endoscopic or radiologic evidence of active disease. At one-year followup, two patients in the treatment group and one patient in the control group achieved remission (p=0.6). There were 76 adverse events were reported in patients receiving HCT and 38 in controls. One HCT patient died.

Lindsay (2017) reported additional analyses on the ASTIC trial participants, combining the treatment patients and the control patients who underwent deferred HCT.^[61] Outcomes were

three-month steroid-free clinical remission at one year and degree of endoscopic healing at one year. Three-month steroid free clinical remission was achieved by 13 of 34 (38%; 95% CI, 22% to 55%) patients who had data available. Complete endoscopic healing was seen in 19 of 38 patients (50%; 95% CI, 34% to 66%). However, serious adverse events (76) were experienced in 23 of 40 patients.

Lindsay (2024) conducted another RCT (ASTIClite) evaluating the effects of reduced intensity conditioning with HCT on Crohn disease.^[62] 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.

Jauregui-Amezaga (2015) evaluated the safety of HCT for the treatment of refractory Crohn's disease in a prospective study that included 26 patients.^[63] The study found very high rates of febrile neutropenia (62% during mobilization and 95% during conditioning). In addition, 12 (57%) patients developed mucositis and two patients experienced hemorrhage.

OTHER AUTOIMMUNE DISEASES

Burt (2020) reported results from a single-center, open-label prospective cohort of 60 patients with chronic inflammatory demyelinating polyneuropathy treated with HCT.^[64] Patients were required to have failed two of three first-line treatments (corticosteroids, intravenous immune globulin, or plasmapheresis). At a median follow-up of 4.5 years, OS was 97%. Medication-free remission at one, two, three, four, and five years was 80, 78, 76, 78, and 83%, respectively. Ambulation-free assistance at one, two, three, four, and five years was 82, 82, 81, 86, and 83%, respectively. No treatment-related mortality occurred, and three (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).

Burt (2019) evaluated HCT for the treatment neuromyelitis optica spectrum disorder in a prospective open-label cohort study.^[65] Thirteen patients were enrolled, of which 11 were aquaporin-4-immunoglobulin G [AQP4-IgG]-positive, one was negative, and one was AQP4-IgG-positive with neuropsychiatric systemic lupus erythematosus. Patients were treated with autologous nonmyeloablative hematopoietic stem cell transplantation. The patient with systemic lupus erythematosus died 10 months post-HCT of complications of active lupus. At a median of 57 months of follow-up, 80% of patients were relapse-free off all immunosuppression ($p < 0.001$).

Greco (2015) evaluated HCT for the treatment of refractory neuromyelitis optica in a retrospective study ($n=16$) using registry data.^[66] After a median follow-up period of 47 months, 3/16 (~19%) patients had progression-free disease and were also no longer receiving treatment, indicating that majority of patients continued to progress or relapse over the long term.

Vanikar (2012) reported the results of a small prospective study ($n=11$) on the use of allogeneic HCT for treatment of Pemphigus vulgaris (PV).^[67] However, patient selection criteria, length of follow-up, and overall survival (or other primary health outcomes) were not stated. Therefore, interpretation of the treatment benefit reported in the manuscript is unclear.

No other prospective clinical trials of sufficient size were identified for the use of HCT in other autoimmune diseases (including immune cytopenias, relapsing polychondritis, and others).

PRACTICE GUIDELINE SUMMARY

AMERICAN SOCIETY FOR TRANSPLANTATION AND CELLULAR THERAPY

In 2020, the American Society for Transplantation and Cellular Therapy (ASTCT) (previously the American Society for Blood and Marrow Transplantation [ASBMT]) issued guidelines on indications for autologous and allogeneic hematopoietic cell transplantation (HCT).^[68] The recommendations listed for systemic sclerosis and multiple sclerosis match their previous recommendations, below. In addition, for rheumatoid arthritis and systemic lupus erythematosus in adults they provide a recommendation of N (not generally recommended) for allogeneic transplant and D (developmental) for autologous transplant; and for juvenile rheumatoid arthritis and systemic lupus erythematosus in pediatric patients, they provide a recommendation of D for allogeneic transplant and R (Standard of care, rare indication) for autologous transplant.

In 2018, the ASBMT published an evidence-based position statement on systemic sclerosis as an indication for autologous hematopoietic cell transplantation.^[69] Based on the results of three RCTs and follow-up meta-analyses, they rate the evidence as high-quality and recommend systemic sclerosis as a “standard of care” indication for autologous HCT.

In 2019, the ASBMT published an evidence-based position statement on autologous hematopoietic cell transplantation for treatment-refractory relapsing multiple sclerosis.^[70] Based on a review of eight retrospective studies, eight clinical trials, and three meta analyses/systematic reviews, the ASBMT recommends considering treatment-refractory relapsing MS with high risk of future disability a "standard of care, clinical evidence available" indication for autologous HCT.

SUMMARY

Medically Necessary

There is enough research to show that hematopoietic cell transplantation (HCT) can improve health outcomes in some individuals with systemic sclerosis/scleroderma. In addition, clinical guidelines based on evidence recommend HCT for treatment of systemic sclerosis. Therefore, HCT may be considered medically necessary for treatment of systemic sclerosis/scleroderma when criteria are met.

Investigational

There is not enough research to show that hematopoietic cell transplantation (HCT) can improve health outcomes in individuals with systemic sclerosis/scleroderma when criteria are not met. Therefore, HCT is considered investigational for treatment of systemic sclerosis/scleroderma when criteria are not met.

There is not enough research to show that hematopoietic cell transplantation (HCT) can improve health outcomes in individuals with other autoimmune diseases. Therefore,

autologous or allogeneic HCT is considered investigational for treatment of autoimmune diseases except systemic sclerosis/scleroderma.

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CODES

Codes	Number	Description
CPT	38204	Management of recipient hematopoietic cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic
	38206	;autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage

Codes	Number	Description
	38208	;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
	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
	38242	Allogeneic lymphocyte infusions
HCPCS	S2140	Cord blood harvesting for transplantation; allogeneic
	S2142	Cord blood derived stem-cell transplantation, allogeneic
	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)

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