

Hematopoietic Cell Transplantation for Autoimmune Diseases

Effective: January 1, 2019

Next Review: April 2019

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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

- I. Autologous 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)
 - O. Systemic sclerosis (i.e., scleroderma)
- II. 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
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 - M. Rheumatoid arthritis (RA)
 - N. Systemic lupus erythematosus (SLE)
 - O. Systemic sclerosis (i.e., scleroderma)

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

CROSS REFERENCES

1. [Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant](#), Transplant, Policy No. 45.03

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 stem 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 HSCT 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 HSCT 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 HSCT 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 HSCT 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 HSCT from 1997 to 2009.^[5] Data for 69 patients were reported (representing less than 1% of the total number of patients treated with HSCT 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 (MS)

A 2011 systematic review evaluated the safety and efficacy of autologous HSCT in patients with progressive MS refractory to conventional medical treatment.^[6] 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 HSCT, 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% confidence interval [CI] 69.9-86.5%) with a median follow-up of 39 months, while the estimate for patients who received a high-dose regimen was 44.6% (95% CI 26.5-64.5%) 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.^[7] At 12-months follow-up, there was a statistically significant decrease in the 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.

Muraro (2017) reported long-term outcomes after autologous HSCT for MS in a large, multi-center cohort.^[8] This study included patients that were treated between 1995 and 2006 that had sufficient data for analysis, including the Expanded Disability Status Scale (EDSS) score at baseline, information on conditioning and graft methods, and at least one follow-up report after transplant. Data for 281 patients were obtained from 25 centers in 13 countries. The majority (218/281) of patients had progressive MS. Overall, the five-year probability of

progression-free survival (by EDSS score) was 46% (95% CI, 42%-54%) and total survival was 93% (95% CI, 89%-96%). Disease progression after transplant was associated with increased age (hazard ratio [HR], 1.03; 95% CI, 1.00-1.05), progressive as opposed to relapsing form of MS (HR, 2.33; 95% CI, 1.27-4.28), and three or more previous disease-modifying therapies (HR, 1.65; 95% CI, 1.10-2.47). A lower baseline EDSS score was associated with improved overall survival (HR, 2.03; 95% CI, 1.40-2.95).

Atkins (2016) tested a regimen of strong immunosuppression followed by autologous HSCT in a phase II single-arm trial at three Canadian hospitals.^[9] This study included 24 patients, aged 18-50, with a baseline EDSS score of 3.0 to 6.0 and a poor prognosis. The primary outcome was disease activity-free survival, and the median follow-up time was 6.7 years (range, 3.9-12.7). At three years after transplant, the proportion with disease activity-free survival was 69.6% (95% CI 46.6-84.2). After up to 13 years of post-transplant follow-up, 35% of patients had durable improvements in their EDSS score, and the rate of brain atrophy in patients decreased to that seen in healthy individuals. One patient died due to transplant complications.

Burman (2017) conducted a registry-based study of autologous HSCT for pediatric MS patients.^[10] 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.

A single-center case series by Burt (2015) reported on 151 patients, 123 with relapsing-remitting MS and 28 with secondary progressive MS.^[11] Patients were treated with nonmyeloablative HSCT between 2003 and 2014. Six patients were not included in the outcome analysis. The remaining 145 patients were followed for a median of two years (range, six months to five years). There were no treatment-related deaths. The primary outcome was change in the EDSS score. A decrease of at least 1.0 point was considered significant improvement and an increase of at least 1.0 point was considered significant progression. There was 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 three, four, and five years. In post hoc analysis, patients most likely to have statistically significant improvements in EDSS score were those with relapsing-remitting MS, with duration of disease of ten years or less, and those without sustained fever during HSCT.

A multicenter case series by Burman (2014) reported on 48 patients with aggressive relapsing-remitting MS, defined as disease with high relapse frequency, and who failed conventional therapy.^[12] Patients underwent autologous HSCT. At the 5-year follow-up, relapse-free survival was 87% and the EDSS score PFS (EDSS deterioration of <0.5 points) was 77%. The rate of disease-free survival (no relapses, no new MRI lesions, no EDSS score progression) was 68%. There was no mortality. The most common long-term side effects were herpes zoster reactivation (15%) and thyroid disease (8.4%).

Burt (2009) transplanted 21 patients with relapsing-remitting MS with ongoing relapses during treatment with interferon.^[13] 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 1-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.^[14]

The EBMT autoimmune diseases working party database published results on a retrospective study of 178 patients with MS who underwent autologous HSCT.^[15] After median follow-up of 42 months, the disease remained stable or improved in 63% of the group. In sub-group analysis, autologous HSCT 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 HSCT is not established in MS or other autoimmune diseases.^[16-18]

Fassas (2011) reported the long-term results of a Phase I/II study conducted in a single center that investigated the effect of HSCT in the treatment of MS.^[19] The authors reported on the clinical and MRI outcomes of 35 patients with aggressive MS treated with HSCT after a median follow-up period of 11 (range 2-15) 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: 0-22) and two years (0-6). Improvements by 0.5-5.5 (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-HSCT. The authors concluded that HSCT 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 HSCT 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 HSCT with reduced-intensity conditioning regimen in 95 patients with different types of MS.^[20] 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. HSCT 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.^[21] Among the other patients, 29 (45%) were stable and five (7%) experienced worsening disease.

Mancardi (2012) reported their experience with 74 consecutive patients with MS treated with autologous HSCT with an intermediate intensity conditioning regimen in the period from 1996 to 2008.^[22] Clinical and MRI outcomes were reported. The median follow-up period was 48.3

months (range=0.8-126). Two patients (2.7%) died from transplant-related causes. After five years, 66% of patients remained stable or improved. Among patients with a follow-up longer than one year, eight out of 25 subjects with a relapsing-remitting course (31%) had a 6-12 months confirmed EDSS improvement >1 point after HSCT, as compared with one out of 36 (3%) patients with a secondary progressive disease course (p=0.009). Among the 18 cases with a follow-up longer than seven years, eight (44%) remained stable or had a sustained improvement, while 10 (56%), after an initial period of stabilization or improvement with a median duration of 3.5 years, showed a slow disability progression.

Bowen (2012) reported the long-term safety and effectiveness of high-dose immunosuppressive therapy followed by autologous HSCT in advanced MS.^[23] Neurologic examinations, brain MRI and cerebrospinal fluid (CSF) for oligoclonal bands (OCB) were serially evaluated. There were 26 patients with a mean EDSS of 7.0; 17 with secondary progressive MS, eight with primary progressive, and one with relapsing/remitting. Median follow up was 48 months after HSCT. The 72-month probability of worsening ≥ 1.0 EDSS point was 0.52 (95% CI: 0.30-0.75). Five patients had an EDSS at baseline of ≤ 6.0 ; four of them had not failed treatment at last study visit. OCB in CSF persisted with minor changes in the banding pattern. Four new or enhancing lesions were seen on MRI, all within 13 months of treatment. In this population with high baseline EDSS, a significant proportion of patients with advanced MS remained stable for as long as seven years after transplant. Non-inflammatory events may have contributed to neurologic worsening after treatment. HSCT may be more effective in patients with less advanced relapsing/remitting MS.

In a small, phase II, RCT (n=21), Mancardi (2015) reported results of the effect of HSCT compared with mitoxantrone on disease variables in patients with severe MS.^[24] Patients were randomized to either receive intense immunosuppression with a combination of drug therapy, followed by HSCT 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 HSCT 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.

A small case series^[25] evaluated patients with relapsing-remitting MS (n=123) or progressive MS (n=28), who were followed for up to five years. Patients were treated with cyclophosphamide and alemtuzumab (n=22) or cyclophosphamide and thymoglobulin (n=129), followed by HSCT infusion. The primary outcome was the change in disability (measured by the Expanded Disability Status Scale [EDSS]). A mean follow-up of 2.5 years, results showed that EDSS scores improved significantly (P<0.001 at each follow-up assessment). In addition, there was significant improvement in disability in a total of 41 patients at two years (50%; 95% CI, 39% to 61%) and in a total of 23 patients at four years (64%; 95% CI, 46% to 79%). The relapse-free survival at four years was 80% and the progression-free survival was 87%. Secondary measures of quality of life (QOL) also showed significant improvement from baseline. Study authors emphasized that although significant improvements were observed in neurological disability, randomized and comparative trials are necessary to confirm these findings.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

A systematic review by Leone (2017) evaluated the use of HSCT in SLE and antiphospholipid syndrome (APS).^[26] 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 HSCT, 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 HSCT as salvage treatment in 50 patients (mean age 30; 43 women, seven men) with SLE refractory to standard care.^[27] 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 5-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 HSCT 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.^[28]

A report from the EBMT Autoimmune Disease Working Party on the variables associated with development of a secondary autoimmune disease following autologous HSCT in a group of 347 patients (with various primary autoimmune diseases) identified SLE as a risk factor for this complication (using multivariate analysis).^[29] 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

The results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published in June 2014.^[30] 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, 0-51 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 HSCT support (n=79) or 12 monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m²). Median follow-up was 5.8 years (interquartile range, 4.1-7.8 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 HSCT 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 HSCT 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 HSCT group (p value unknown). Time-varying hazard ratios (modeled with treatment x time interaction) for event-free survival were 0.35 (95% CI, 0.15-0.74) at two years and 0.34 (95% CI, 0.16-0.74) at four years, supporting a benefit of HSCT versus pulsed cyclophosphamide. Severe or life-threatening grade 3 or 4 adverse events were reported in 51 (63%) of the HSCT 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 HSCT compared with the standard of care for systemic sclerosis.^[31] 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 HSCT, 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 HSCT 12 months after enrollment. No deaths occurred in either group during follow-up. Patients allocated to HSCT (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 HSCT (p=0.0001). After long-term follow-up (mean 2.6 years) of patients who were allocated to HSCT, 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 HSCT without complication, and all improved after HSCT. 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 HSCT suggested that the improvements in mRSS (p<0.0001) and forced vital capacity (p<0.03) persisted.

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.

Vonk (2008) reported the results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HSCT from 1998 to 2004.^[32] There was one transplant-related death and one death due to progressive disease, leaving 26 patients for evaluation. After a median follow-up of 5.3 years (range, 1–7.5), 81% (n=21/26) of the patients demonstrated a clinically beneficial response. Estimated survival at five years was 96.2% (95% confidence interval [CI]: 89–100%) and 84.8% (95% CI: 70.2–100%) at seven years. Event-free survival was 64.3% (95% CI: 47.9–86%) at five years and 57.1% (95% CI: 39.3–83%) at seven years.

Nash (2007) reported the long-term follow-up of 34 patients with diffuse cutaneous systemic sclerosis with significant visceral organ involvement who were enrolled in a multi-institutional pilot study between 1997 and 2005 and underwent autologous HSCT.^[33] Overall and progression-free survival both 64% at five years, respectively.

Henes (2012) reported on their experience with autologous HSCT for systemic sclerosis in 26 consecutive patients scheduled for HSCT between 1997 and 2009.^[34] The major outcome variable was the response to treatment (reduction of modified Rodnan skin score [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 6. 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 HSCT resulted in significant improvement in most patients with systemic sclerosis.

JUVENILE ARTHRITIS

A review article by Saccardi (2008) summarized the experience thus far with juvenile idiopathic and rheumatoid arthritis.^[35] 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 HSCT for rheumatoid arthritis has decreased significantly since 2000, due to the introduction of new biologic therapies. Most patients who have undergone HSCT have had persistence or relapse of disease activity within six months of transplant.

TYPE 1 DIABETES

Several case series were identified evaluating autologous HSCT in patients with new-onset type 1 diabetes; there were no published comparative studies. In the series, although a substantial proportion of patients tended to become insulin-free after HSCT, remission rates were high. In 2015, Xiang (2015) 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.^[36] After a mean follow-up of 28.5 months (range, 15-38 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 HSCT 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 HSCT.^[37] Patients had a mean age of 26.5 years (range, 18-34 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, 9.5-80 months). Mean insulin doses remained significantly lower than baseline doses at two and three years, but the insulin doses returned to pre-HSCT levels at years four and 5. 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 HSCT in 23 patients with type 1 diabetes (age range, 13-31 years) diagnosed in the previous six weeks by clinical findings with hyperglycemia.^[38] After a mean follow-up of just over two years (29.8 months; range, 7-58 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.

OTHER AUTOIMMUNE DISEASES

Vanikar (2012) reported the results of a small prospective study (n=11) on the use of allogeneic HSCT for treatment of Pemphigus vulgaris (PV).^[39] 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.

Jauregui-Amezaga (2015) evaluated the safety of HSCT for the treatment of refractory Crohn's disease in a prospective study that included 26 patients.^[40] 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.

Greco (2015) evaluated HSCT for the treatment of refractory neuromyelitis optica in a retrospective study (n=16) using registry data.^[41] 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.

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

No evidence-based clinical practice guidelines were identified on the use of HCT for treatment of autoimmune diseases.

SUMMARY

There is not enough research to show that hematopoietic cell transplantation (HCT) can improve health outcomes in patients with autoimmune disease. In addition, no clinical guidelines based on research recommend the use of HCT for any autoimmune diseases. Therefore, autologous or allogeneic HCT is considered investigational for treatment of any autoimmune disease.

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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
	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
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	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
	38243	;HPC boost
38242	Allogeneic lymphocyte infusions	
HCPCS	J9000– J9999	Chemotherapy drugs code range
	Q0083– Q0085	Chemotherapy administration code range
	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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