Stem-Cell Transplantation for Autoimmune Diseases/Miscellaneous Conditions

Table of Contents

Coverage Policy .................................................. 1
Overview .............................................................. 2
General Background ........................................... 2
Coding/Billing Information ........................................ 10
References .......................................................... 11

Related Coverage Resources

Extracorporeal Photopheresis

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Coverage Policy

Hematopoietic stem-cell transplantation (HSCT) for the treatment of ANY of the following autoimmune diseases is considered experimental, investigational or unproven:

- autoimmune hemolytic anemia
- autoimmune hepatitis
- celiac disease
- Crohn’s disease
- cryptogenic cirrhosis
- dermatomyositis
- immune vasculitis
- juvenile idiopathic arthritis
- multiple sclerosis
- neuromyelitis optica
- polymyositis
- rheumatoid arthritis
- systemic lupus erythematosus
- systemic sclerosis, also known as scleroderma
- thrombotic thrombocytopenia purpura
• type I diabetes mellitus
• ulcerative colitis

HSCT for the treatment of type 2 diabetes mellitus is considered experimental, investigational or unproven.

Overview

This Coverage Policy addresses allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of autoimmune disease and type 2 diabetes mellitus.

Autoimmune diseases are a group of highly varied disorders which develop when the immune system attacks healthy cells. Crohn’s disease, juvenile idiopathic arthritis, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis and type 1 diabetes mellitus are some of the more common types of autoimmune diseases.

Type 2 diabetes mellitus is the most common form of diabetes. With this disorder the pancreas makes insulin but doesn’t use it efficiently and blood glucose levels rise higher than normal.

Hematopoietic stem-cell transplantation (HSCT) has been proposed as a treatment for autoimmune diseases and for type 2 diabetes mellitus. HSCT involves taking hematopoietic stem cells that can regenerate all the blood cells normally produced in the bone marrow from the bone marrow or blood of a donor and infusing them into the person with the disorder, following medication to suppress the immune system.

General Background

Autoimmune diseases are a very heterogeneous group of disorders with varying etiologies, levels of organ involvement and prognosis (Burt, 2008). Standard treatment for autoimmune diseases generally consists of immunosuppression, anti-inflammatory and/or anti-malarial medication, and supportive care. Dose escalation of immunosuppressive medication utilizing hematopoietic stem-cell transplantation (HSCT) has been proposed for individuals who are refractory to standard treatment or have disease considered to be life-, or organ-threatening.

The peer-reviewed, published scientific research consists of retrospective analyses, small case studies, feasibility studies, and phase I/II trials that limit the ability to generalize findings to the population of individuals with autoimmune diseases; however, a number of phase III clinical trials are ongoing. Non-standard patient selection criteria, small patient populations, variability of conditioning regimens used for transplantation and lack of randomization are reported limitations of many published studies. Although results of published studies are promising, in the absence of outcomes from well-designed randomized controlled trials published in peer-reviewed scientific literature, the role of HSCT for any autoimmune disease has not yet been established. Likewise, there are insufficient data to demonstrate improved outcomes with hematopoietic stem-cell transplantation (HSCT) for the treatment of type 2 diabetes mellitus (DM).

Hematopoietic Stem-Cell Transplantation (HSCT)

Stem-cell transplantation refers to transplantation of hematopoietic stem cells (HSCs) into a patient. HSCs are immature cells that can develop into any of the three types of blood cells (red cells, white cells or platelets). HSCT can be either autologous (i.e., using the patient’s own stem cells), or allogeneic (i.e., using stem cells from a donor).

The goal of HSCT for autoimmune diseases is to generate self-tolerant lymphocytes with lymphoablation rather than to ablate and reconstitute the entire hematopoietic system (i.e., myeloablation) (Burt, 2006). The intense immunosuppression used with HSCT, which approaches or exceeds the myeloablation level, is thought to eliminate T-cells which cause the autoimmune response. It is also theorized that the regeneration of bone marrow with transplanted stem cells normalizes the immune system, possibly by the elimination of self-reactive lymphocytes from the patient and the creation of a tolerant immune system (Tyndall and Gratwohl, 2000).
Conditioning regimens used with allogeneic HSCT for autoimmune diseases are designed to suppress the recipient immune response while causing minimal toxicity and may be myeloablative or nonmyeloablative (i.e., lympho/immunoablative) in dosage. Very high doses of immunosuppressive chemotherapy may cause myelosuppression, necessitating rescue with transfused hematopoietic stem cells; most commonly, autologous cells are used. In some studies, treatment-related mortality (TRM) rates of individuals who have undergone autologous HSCT for autoimmune disorders have been noted to be higher than the rates in patients with non-autoimmune diseases; 5%–15% versus 1%–5%, respectively (Nikolov, 2008).

The effectiveness of myeloablative or lymphoablative conditioning and HSCT for any autoimmune disorder remains unclear. Additionally, the occurrence of new autoimmune phenomena has been described after allogeneic and autologous HSCT, including the production of autoantibodies, autoimmune thyroid disease, cytopenias, autoimmune hemolytic anemia, and myasthenia gravis. The underlying mechanisms are not well understood, but graft-versus-host disease and homeostatic expansion following transplantation-induced lymphopenia has been implicated (Daikeler, 2011; Nikolov, 2008).

**Literature Review**

The feasibility of allogeneic hematopoietic stem-cell transplantation (HSCT) for autoimmune diseases was discussed at a 2005 workshop sponsored by the National Institute of Allergy and Infectious Diseases and the National Cancer Institute. The participants concluded that experience is clearly insufficient to allow reliable extrapolation of data on safety and risks from patients with malignancies to patients with autoimmune disease. Workshop participants determined that it is not possible to definitely recommend one transplantation regimen over another and recommended that planning be initiated for clinical trials to generate safety and efficacy data for allogeneic hematopoietic cell transplantation in patients with severe autoimmune diseases (Griffith, 2005).

Several retrospective trials have been published in the peer-reviewed scientific literature in which study populations were heterogeneous, including individuals with multiple sclerosis (MS), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and/or immune thrombocytopenia within the same study (Snowden, 2011; Farge, 2010; Loh, 2007; Gualandi, 2007; Gratwohl, 2005; Gratwohl, 2004). Variability of diagnoses, non-standard patient eligibility criteria, wide range of conditioning regimens, and lack of randomization are limitations to these studies and make it difficult to determine the effectiveness of this therapy for specific indications.

Snowden et al. (2011) retrospectively analyzed outcomes of autologous and allogeneic HSCT for autoimmune disease from British Society of Blood and Marrow Transplantation registry data. Fifty-five autologous and 15 allogeneic HSCTs were registered. Overall survival (OS) at one and five was 85% and 78%, respectively, in the autologous group and 87% and 65%, respectively, in the allogeneic group. Progression-free survival (PFS) at one and five years was 51% and 33%, respectively, in the autologous group and 80% and 65%, respectively, in the allogeneic group.

Farge et al. (2010) reported results of a retrospective observational study involving all first HSCT for autoimmune diseases reported to the European Group for Blood and Marrow Transplantation (EBMT) registry between 1996 and 2007 (n=900). Of these, MS (n=345), SSc (n=175), SLE (n=85), RA (n=89), JIA (n=65), and immune cytopenia (n=37) were the most frequently occurring diagnoses transplanted. Among all patients, the five-year survival was 85% and the progression-free survival was 43%, although the rates varied widely according to the type of autoimmune disease. At the time of study analysis, 789 patients were alive and 111 had died: 43 (38.7%) from their original disease and 59 (53.1%) from transplantation-related causes. Five years after HSCT, the progression-free survival (PFS) was 45% for multiple sclerosis (MS), 55% for systemic sclerosis (SSc), 18% for rheumatoid arthritis (RA), 44% for systemic lupus erythematosus (SLE), 52% for juvenile idiopathic arthritis (JIA) and 34% for immune cytopenia. Five-year OS was 92% for MS, 76% for SSc, 94% for RA, 76% for SLE, 82% for JIA, and 80% for immune cytopenia. No significant influence of transplant technique was identified. The authors noted that these data support ongoing and planned phase III trials to evaluate the place of autologous HSCT in the treatment strategy for severe autoimmune diseases.

Published peer-reviewed data are scarce regarding the safety and effectiveness of autologous or allogeneic HSCT for the treatment of autoimmune hemolytic anemia, celiac disease, cryptogenic cirrhosis, dermatomyositis, immune vasculitis, neuromyelitis optica, polymyositis, thrombotic thrombocytopenia purpura, and ulcerative
colitis. Additional clinical studies investigating specific autoimmune diseases include but are not limited to, the following:

**Crohn’s Disease (CD):** There are limited published, peer-reviewed clinical trial data regarding the safety and effectiveness of HSCT to improve outcomes for individuals with Crohn’s disease. Additional randomized controlled clinical trials are needed. At this time the role of HSCT has not been determined for this indication.

Hawkey et al. (2015) reported outcomes of a randomized clinical trial Autologous Stem Cell Transplantation International Crohn Disease (ASTIC) conducted in 11 European transplant units for 45 patients with refractory Crohn disease not amenable to surgery despite treatment with ≥ 3 immunosuppressive or biologic agents and corticosteroids. All patients underwent stem cell mobilization before 1:1 randomization to intermediate-intensity conditioning with immunoablation and HSCT (n = 23) or control treatment (HSCT deferred for 1 year [n = 22]). Primary endpoint was sustained disease remission at one year characterized by: clinical remission (Crohn Disease Activity Index (CDAI) <150), no use of corticosteroids or immunosuppressive or biologic drugs for at least the last three months, and no endoscopic or radiological evidence of active (erosive) disease anywhere in the gastrointestinal (GI) tract. Secondary outcomes were individual components of the primary composite outcome and other measures of disease activity, laboratory results, quality of life and functional status, and GI tract imaging. During follow-up, all patients in either trial group could receive standard care for Crohn disease, including corticosteroids, immunosuppressive agents, and biologic therapy. Sustained disease remission was achieved in two patients undergoing HSCT (8.7%) versus one control patient (P = .60). Fourteen patients undergoing HSCT (61%) vs five control patients (23%) had discontinued immunosuppressive or biologic agents or corticosteroids for at least three months (P = .01). Ten vs two patients had a CDAI less than 150 (remission) at the final evaluation, eight (34.8%) versus two (9.1%) for three or more months (P = .052). Eight (34.8%) versus 2 (9.1%) patients were free of active disease on endoscopy and radiology at final assessment (P = .054). There were 76 serious adverse events in patients undergoing HSCT versus 38 in controls. One patient undergoing HSCT died. Authors note among adult patients with refractory Crohn disease HSCT did not result in a statistically significant improvement in sustained disease remission at one year and was associated with significant toxicity. Authors also noted did not support the widespread use of HSCT for patients with refractory Crohn disease.

In a follow-up study Lindsay et al. (2017) reported a pooled analysis of data from the ASTIC study (n=40) for any patient who received HSCT (i.e., immediate transplantation per ASTIC study protocol (n=23) plus 17 patients who received conventional care plus delayed (i.e., at one year) autologous HSCT. The primary outcome for this analysis was three-month steroid-free clinical remission at one year after HSCT (Crohn’s Disease Activity Index (CDAI) <150). Participants were not masked to treatment, but the adjudication panel that reviewed radiology and endoscopy was masked to allocation and visits. At one year after HSCT, 3-month steroid-free clinical remission was seen in 13 (38%) of 34 patients with available data for the whole year. On multivariate analyses, factors associated with the primary outcome were short disease duration (p=0.048) and low baseline CDAI (p=0·031). Seventy-six treatment-related adverse events occurred in 23 of 40 patients with available data. The most common serious adverse event was infection, most of which were treatment related. Smoking and perianal disease at baseline were independent factors associated with the number of serious adverse events.

Burt et al. (2011) performed a retrospective analysis of long-term outcomes of 24 patients, including 12 patients in a previous Phase I study. Clinical relapse-free survival (i.e., the percent free of restarting CD medical therapy after transplantation) was 91% at one year, 63% at two years, 57% at three years, 39% at four years, and 19% at five years. At five years the percentage of patients in remission, steroid-free, or medication-free at any post-transplantation evaluation interval remained ≥ 70%, 80%, and 60%, respectively. Study limitations that preclude the ability to translate these results to standard clinical practice include uncontrolled design and small patient numbers.

In a previous Phase I study involving immune ablative HSCT in 12 patients with refractory Crohn’s disease, Burt et al. (2006) reported improvement in symptoms and the Crohn’s Disease Activity Index (CDAI) prior to hospital discharge. Improvement in radiographic and colonoscopy findings occurred over months to years following HSCT. Eleven of 12 patients entered a sustained remission defined by a CDAI <150. After a median follow-up of 18.5 months, only one patient developed a recurrence of active CD, which occurred 15 months after HSCT. The authors noted that a randomized study was needed to confirm the effectiveness of this study.
Juvenile Idiopathic Arthritis (JIA): Randomized controlled clinical trial data are lacking. Small studies with uncontrolled design have reported a drug-free remission of disease in up to 36% of patients up to five years (Brinkman, 2007; Wulffraat, 2005). In the study by Brinkman et al., at a median follow-up of 80 months, 68% of patients achieved a sustained remission or significant improvement. Treatment-related mortality was 9%. After fatal complications due to macrophage activation syndrome were observed in several patients, the protocol was amended to ensure less profound depletion of T cells, better control of disease prior to transplantation, antiviral prophylaxis, and slower tapering of corticosteroids. The five-year probability of overall survival (OS) was 82%. The probability of disease-free survival (DFS) at five years was 36%. Study limitations include small patient numbers, nonrandomized trial design, and change in treatment protocol during the study.

Although published outcomes are promising, lack of randomization and small participant populations limit the ability to determine the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for the treatment of juvenile idiopathic arthritis (JIA). The role of HSCT for this indication has not yet been established.

Multiple Sclerosis (MS): Results of prospective clinical trials, retrospective analyses, case series and cohort studies have been published reporting the safety and effectiveness of autologous HSCT for the treatment of MS. In several studies improvement in the Expanded Disability Scale Scores (EDSS) following transplantation was reported for a majority of patients (Sormani, 2017; Burman, 2017; Casanova, 2017; Nash, 2017; Atkins, 2016; Burt, 2015; Shevchenko, 2015; Burt, 2009; Fagius, 2009; Shevchenko, 2008; Portaccio, 2007; Saccardi, 2006; Ni, 2006; Su, 2006). Although results of published studies are promising, the ability to translate these results to the wider population of individuals with MS is limited by heterogeneous patient selection criteria and patient diagnosis, small population size, study design (e.g., lack of randomization for some studies), and short follow-up. Randomized clinical trials are ongoing for this indication. At this time the role of HSCT has not yet been established for treatment of multiple sclerosis.

Shevchenko et al. (2015) reported long-term outcomes of a prospective single center study enrolling 99 individuals with multiple sclerosis (relapsing/remitting MS, n=43; progressive MS, n=56) who received autologous HSCT with reduced-intensity conditioning. Patients received one of two conditioning regimens. Neurological assessment using EDSS and Quality of Life assessment using the RAND SF-36 questionnaire was performed at baseline; at discharge; at three, 6, 9, and 12 months after transplantation; every 6 months thereafter up to 48 months; and then at yearly intervals. Magnetic resonance imaging (MRI) scans of the brain and spinal cord with gadolinium (Gd) enhancement were also performed at these same intervals. At eight years after AHSCT, 16.7% of cases progressed.

Long-term outcome analysis was performed in 64 patients with at least 36 months follow-up post-transplant; median follow-up: 62 months. Forty-seven percent improved at least 0.5 point on the EDSS scale compared to baseline. All patients who did not have disease progression or relapse were off therapy throughout the post-transplant period. Results of MRI scan results were available in 55 patients. At six months after HSCT, in the group of patients with active lesions at baseline, lesions became inactive in 14 of 15 cases. In the group without active lesions pre-transplant, 39 of 40 remained inactive. At the median of 26 months post-transplant in the group with Gd-enhancing lesions at baseline, there were three cases of disease progression and in the group without active lesions at baseline, three patients had disease progression. Important limitations to the study include non-randomized design, variations in previous treatment received by study participants, differences in chemotherapy regimens used for conditioning and that not all patients were included in long-term analysis. Although results of this study suggest improved outcomes, randomized controlled trials are needed to determine the role of high-dose immunosuppressive therapy and autologous transplantation for treatment of multiple sclerosis.

Atkins et al. (2016) reported results of a prospective Phase II clinical trial of 24 patients with multiple sclerosis who received immunoablation with busulfan, cyclophosphamide, and rabbit anti-thymocyte globulin followed by autologous HSCT. Primary outcome was multiple sclerosis activity-free survival at three years after stem-cell transplantation. Secondary outcomes were time to treatment failure (relapse or progression), overall survival, transplantation-related mortality, transplantation-related morbidity, immunological reconstitution, hematopoietic reconstitution and MRI-related changes in disease activity (new and Gd-enhancing lesions as well as atrophy). Twenty-one patients completed three-year follow-up. Median follow-up was 6.7 years. Three-year multiple
sclerosis activity-free survival was 69.6%. With up to 13 years of follow-up after HSCT, no relapses occurred and no Gd-enhancing lesions or new T2 lesions were seen on 314 MRI sequential scans. The rate of brain atrophy decreased to that expected for healthy controls. One of 24 patients died of transplantation-related complications. Thirty-five percent of patients had a sustained improvement in their Expanded Disability Status Scale score.

Nash et al. (2017) described results of a prospective phase II clinical trial (HALT-MS) of high-dose immunosuppression and autologous HSCT for multiple sclerosis for patients with relapsing-remitting (RR) MS who experienced relapses with disability progression while on MS disease-modifying therapy. The primary endpoint was event-free survival (EFS), defined as survival without death or disease activity from any one of: disability progression, relapse, or new lesions on MRI. Participants were evaluated through 5 years post-transplant. Median follow-up was 62 months. The estimated EFS probability was 73.8% at 4 years and 69.2% at 5 years. Of 24 participants transplanted, seven did not maintain EFS by close of follow-up by an increase in EDSS. 0.5, clinical relapse (n=3), or development of new MRI lesions (n=2). The five-year progression-free survival was 91.3%, relapse-free survival was 86.9%, MRI activity-free survival was 86.3% and overall survival was 86.3%.

There were no significant late neurologic adverse effects noted. Improvements were noted in neurologic disability with a median change in EDSS of -0.5 (P=0.001) among participants who survived and completed the study.

Burman et al. (2017) reported results of a retrospective analysis of data reported to the European Society for Blood and Marrow Transplantation registry. Twenty-one patients with MS received autologous HSCT with one of two conditioning regimens. All patients had previously been treated with at least one disease-modifying drug, 11 received at least two disease-modifying drugs and four received > two previous treatments. The median follow-up time after HSCT was 2.8 years. Treatment-related mortality was zero. Three year PFS was 100% based on Expanded Disability Status Scale (EDSS) scores. Median EDSS score was 2.0 (range 0-8) compared with a score of 6 prior to transplantation. Three patients experienced a clinical relapse or had subclinical post HSCT, with appearance of new gadolinium-enhancing lesions. Data were missing for three additional patients. Four patients who had follow-up for 10 years had no record of recurring disease activity. Post-HSCT treatment related to MS was required in six patients. Study limitations include small study participant number, incomplete data and retrospective study design.

Using retrospective analysis Casanova et al. (2017) described the long-term results of myeloablative autologous HSCT in 38 individuals with multiple sclerosis (relapsing/remitting MS n= 28, secondary progressive MS n=10), transplanted between 1999 and 2015. Thirty-one patients followed at least 24 months were selected to analyze efficacy; median follow-up of patients alive was 8.4 years. Mean age at transplant was 36.7 years. Prior to transplantation the EDSS was high in the individuals with SPMS, and the number of relapses was significantly higher in individuals with RRMS. Transplant-related mortality was zero. In long-term follow-up, three solid tumors were diagnosed: two breast carcinomas and one cervical intraepithelial neoplasm grade 2, with median time to diagnosis of 5.1 years. The annualized relapse rate (ARR) was zero in the first year, 0.22 in the second year, stable until year five and then was 0.05 in years six and seven. A total of 10 patients (32.3%) had at least one relapse post-transplantation. After transplant, RRMS patients showed a sustained improvement in the EDSS, while patients with SPMS remained Stable the first year and then continued to progress. Seven patients (22.6%) experienced progression of disability. Some type of disease activity was observed in 14 patients post transplantation. Sustained recovery of disability defined as the improvement of 1.0 for 6 months was reached in 60% of individuals with RRMS patients for 7 years after AHSC, 40% remained stable with no worsening of disability. Study limitations include small participant numbers, heterogeneous conditioning regimens and retrospective study design.

Burt et al. (2015) reported results of a case series involving all patients undergoing nonmyeloablative allogeneic HSCT for relapsing-remitting MS (n = 123) or secondary-progressive MS (n = 28) at one facility between 2003 and 2014. Primary objective was to determine the association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability and other clinical outcomes in patients with MS. Outcome analysis was available for 145 patients with a median follow-up of 2 years and a mean of 2.5 years. Scores from the EDSS improved significantly from pretransplant to two years (n=82) to four years (n=23) (p<001 at each assessment). A significant decrease in disability was reported based on the EDSS at two years (n=41) and four years (n=23). Four-year relapse-free survival was 80% and progression-free survival was 87%. Neurological
rating scale also improved at two and four years (p<.001). Total quality-of-life scores improved significantly at
two-year follow-up (n=132, p<.001). There was a decrease in T2 lesion volume from pretransplant to the last
post-transplant assessment (mean 27 months, n=128, p<.001). Data suggest improved outcomes in this case
series.

Burt et al. (2009) also reported on the results of a phase I/II trial of autologous nonmyeloablative HSCT in 21
patients. Seventeen of twenty-one patients demonstrated improvement by at least one point on the Kurtzke
Expanded Disability Status Scale (EDSS). Five patients relapsed but achieved remission after further
immunosuppression. After a mean of 37 months, all patients showed significant improvement in neurological
disability as demonstrated by the EDSS, neurological rating scale score, paced auditory serial addition test, and
25-foot walk test.

Somani et al. (2017) reported pooled results of a meta-analysis of 15 studies including 764 transplanted patients
with multiple sclerosis who received low (n=2 studies), intermediate (n=8), high- (n=4) or mixed (i.e., low intensity
or intermediate intensity, n=1) conditioning immunoablation and autologous HSCT. The pooled estimate of TRM
was 2.1%. TRM was higher in older studies (p=0.014) and in studies with a lower proportion of patients with
relapsing-remitting MS (RRMS) (p=0.028). A higher baseline Expanded Disability Status Scale (p=0.013) was
also significantly associated with a higher TRM. Pooled rate of progression was 17.1% at 2 years and 23.3% at 5
years. Lower two-year progression rate was significantly associated with higher proportions of patients with
RRMS (p=0.004). The pooled proportion of patients at two years with no evidence of disease activity was 83%
and 67% at five years. Heterogeneous patient eligibility, intensity and type of conditioning regimens and
uncontrolled design of included studies limit the ability to inform on health benefits with autologous HSCT.

Reston et al. (2011) performed a systematic review of eight case series studies involving 161 enrolled individuals
with progressive multiple sclerosis refractory to alternative treatments. Follow-up was a median of 24 months.
Studies met inclusion criteria based on a primary outcome for PFS. Six additional studies were evaluated for a
summary of morbidity and mortality. Compared with high-intensity conditioning regimens, intermediate-intensity
immunoablative therapy with autologous bone marrow/peripheral stem-cell transplantation was associated with
higher progression-free survival (PFS) for individuals with secondary progressive multiple sclerosis (MS). There
was insufficient evidence to determine PFS in other types of MS. Treatment-related mortality was 2.7%.

**Rheumatoid Arthritis (RA):** Data are limited in the published peer-reviewed scientific literature. Small trials with
uncontrolled study design limit the ability to determine safety and effectiveness of autologous or allogeneic
HSCT for this indication. The role of HSCT in the treatment of RA has not yet been established.

**Systemic Lupus Erythematosus (SLE):** Although outcomes regarding disease stability are promising, lack of
randomization and uncontrolled study design, and small participant populations limit the ability to apply HSCT as
a standard treatment for SLE. Several clinical trials are ongoing for this indication; the role of HSCT for this
indication has not yet been established.

Randomized controlled clinical trial data are lacking. Several small, prospective trials, an analysis of registry data
and a systematic review have reported stability of disease and improvement in quality of life following HSCT
(Leone, 2017; Alchi, 2013; Su, 2013; Song, 2011; Burt, 2006). Alchi reported outcomes of 28 patients who
underwent autologous HSCT between 2001 and 2008. Five-year overall survival rate was 81%, disease-free
survival was 29%, with a relapse incidence of 56% and non-relapse mortality rate of 15%. In the study by Song
et al., the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to evaluate activity.
SLEDAI scores significantly (p<0.01), although progression-free survival rates were significantly lower in patients
receiving conventional therapy compared with those receiving autologous HSCT. There was no significant
difference in OS. For this study, the authors note that recruitment of more patients into multi-center, randomized,
comparative studies versus conventional treatment of SLE is warranted to assess the efficacy and safety of
autologous HSCT. In the study by Burt et al., (n=50), with a mean follow-up of 29 months, OS was 84%, and
probability of disease-free survival (DFS) at five years following HSCT was 50%. Secondary analysis
demonstrated stabilization of renal function and improvement in SLEDAI score, anti-nuclear antibody (ANA),
antidouble strand deoxyribonucleic acid, complement, and carbon monoxide diffusion capacity. Small patient
population and uncontrolled study design limit the ability to apply these study results to the general population of
individuals with SLE.
The use of allogenic/autologous HSCT as rescue therapy for SLE/antiphospholipid syndrome (APS) was assessed by Leone et al. (2017) using data from two prospective, 10 retrospective studies and 13 case reports, for a total of 279 patients with SLE patients. Of those, 54 patients also fulfilled the classification criteria of APS. The majority of the studies reported an improvement after HSCT in terms of disease activity control or overall survival. One study reported no net benefit of HSCT when compared to immunosuppression alone. One retrospective study reported an overall survival at five-years of 81% in 28 SLE patients. Data reflect 86 infections in the pool of patients (30.8%); three resulted in the death of the patient (1.3%). The authors note results are promising and that further studies are warranted in order to assess the safety of the procedure for both the occurrence of secondary autoimmune disease and the rate of infection. Authors also noted the rate of adverse effects confines this option to selected cases of SLE patients who are resistant or refractory to standard approaches.

Systemic Sclerosis (SSc): Additional phase II and III randomized clinical trials are ongoing. Although results are promising, there is insufficient evidence to support the safety and effectiveness of HSCT for the treatment of SSc; randomized controlled trial data are limited and long-term outcomes are unknown. The role of HSCT has not yet been established for this indication.

Van Laar et al. (2014) reported outcomes of The Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial, a phase 3, multicenter, randomized (1:1), open-label, parallel-group, clinical trial conducted in 10 countries at 29 centers with access to a European Group for Blood and Marrow Transplantation-registered transplant facility between 2001 and 2009. The trial involved 156 patients with early diffuse cutaneous systemic sclerosis. The trial compared HSCT versus intravenous pulse cyclophosphamide. The protocol for HSCT was designed with the intention to achieve intensive lymphocyte ablation. Patients were randomly assigned to receive HSCT (n = 79) or cyclophosphamide (n = 77). Seventy-one (89.8%) and 57 (74.0%) completed treatment in the HSCT and cyclophosphamide groups, respectively. Fifty-three events occurred during the study (HSCT: 19 deaths, three irreversible organ failures; Control: 23 deaths and eight irreversible organ failures). Eight patients died in the first year in the HSCT group versus zero in the control group. The hazard ratios for event-free survival and overall survival were time-varying (p = .04 and p = .03, respectively). Data suggest that HSCT was associated with increased treatment-related mortality in the first year compared with cyclophosphamide. Time-varying hazard ratios for event-free survival were 0.35 (95%CI, 0.16-0.74) at 2 years and 0.34 (95%CI, 0.16-0.74) at 4 years.

Burt et al. (2011) reported outcomes of 19 patients in an open-label, randomized controlled phase II trial of autologous nonmyeloablative HSCT (n=10) compared with the standard of care, cyclophosphamide (n=9). The primary outcome for all enrolled patients was improvement at 12 months’ follow-up, defined as a decrease in modified Rodman skin scores (mRSS) or an increase in forced vital capacity by more than 10%. Patients in the control group with disease progression despite treatment with cyclophosphamide could switch to HSCT 12 months after enrollment. All ten patients randomly allocated to receive HSCT improved at or before 12 months, compared with none of nine allocated to cyclophosphamide (p=0.00001). Eight of nine controls had disease progression (without interval improvement compared to no patients treated by HSCT, p=0.00001). Treatment failure (i.e., disease progression without interval improvement) occurred in eight of nine controls compared with none of 10 patients treated by HSCT (p=0.0001). Data suggest that nonmyeloablative autologous HSCT may improve skin and pulmonary function in patients with systemic sclerosis; however, longer follow-up and data from larger RCTs are needed to determine use compared with conventional dose immunotherapy.

Vonk et al. (2008) reviewed the outcomes of 26 patients with severe diffuse cutaneous SSc who underwent autologous HSCT. Two patients included in the study were later found to have violated the study inclusion criteria; however, their results were included in the analysis. Two patients (7.1%) died within six months of the procedure. The probability of survival of individuals with at least six month follow-up after HSCT was 96.2% at five years; and 84.8% at seven years. After a median follow-up of 5.2 years, death from disease progression occurred in two patients (8%). Event-free survival rates for patients with at least six months of follow-up after transplantation were 64.3% at five years and 57.1% at seven years. Study limitations included lack of randomization, small participant population, and inclusion of data from ineligible participants.
Additional small phase I and II clinical trials (Oyama, 2007; Nash, 2007) reported improvement in skin scores and stable cardiac, pulmonary, and renal function following nonmyeloablative dose immunosuppressive therapy with autologous HSCT. After median follow-up of 25.5 months, the overall survival (OS) and progression-free survival (PFS) rates were 90% and 70%, respectively, as reported by Oyama, with five-year estimated PFS and OS of 64% in the study by Nash.

**Type I Diabetes Mellitus (DM):** High-quality evidence in the form of randomized clinical data in the published peer-reviewed scientific literature is limited. El Badawy et al. (2016) reported results of a systematic review and meta-analysis of 22 eligible clinical trials that satisfied inclusion criteria, with a total of 524 patients with type I or type 2 DM. Considering the source of cells, 6 studies used hematopoietic stem cells (HSCs) (n=149 patients) and five studies used umbilical cord blood (UCB) (n=74). Three studies included a control group. One study included in the analysis was a randomized controlled trial. In four studies, autologous umbilical cord blood (UCB) cells were infused into 71 children with type 1 DM. There was a low incidence of side effects. The functional outcome was uniformly negative as UCB infusion failed to improve C-peptide, HbA1c and insulin utilization levels at 12 months’ post-transplantation. In a total of 6 studies, hematopoietic stem cells were administered to 149 patients with type 1 DM. C-peptide levels were measured in three of the six studies (n=82). The mean C-peptide peak levels significantly increased from 0.55 ng/ml at baseline to 1.09 ng/ml at 6 months after initiation of therapy (p<0.0001). HbA1c levels were determined in three of the seven studies (n=96 patients). The mean level of HbA1c significantly decreased from 10.14% at baseline to 5.94% at 6 months’ post transplantation (p<0.0001). Eighty-six became insulin-free for a mean period of 16 months; in 11 patients the insulin requirement was reduced by more than 50%. Out of the remaining 49 patients with poor prognosis, 39 (79.5%) had diabetic ketoacidosis (DKA). Patients who received the therapy earlier after type I DM diagnosis (within 6 weeks) were twice as likely to achieve insulin independence over time than those with a later diagnosis (p = 0.0008). Thirty-four percent reported mild to moderate side effects with the death of one patient as a result of Pseudomonas aeruginosa sepsis. No studies were analyzed using UCB or HSCs via intravenous central or peripheral infusion for the treatment of DM type 2. Study limitations included the pooling of data from studies with heterogeneous design, including lack of randomization, small participant numbers and short-term follow-up.

Additional phase II and III randomized clinical trials are ongoing. Although results are promising, there is insufficient evidence to establish the role of autologous or allogeneic HSCT for the treatment of type I diabetes mellitus. Professional society support in the form of published consensus guidelines is also lacking.

**HSCT for Type 2 Diabetes Mellitus:** Data in the published, peer-reviewed scientific literature are insufficient to inform on improved outcomes with HSCT. Bhansali et al. (2014) reported results of a prospective, randomized, single-blinded placebo-controlled study involving 21 patients with type 2 diabetes mellitus, triple oral antidiabetic drug failure, requiring insulin ≥0.4 IU per kg per day with HbA1c <7.5%. Patients in the intervention group (n=11) received autologous bone marrow transplantation. After 12 weeks, a second dose of stem cells was administered. The control group (n=10) underwent bone marrow aspiration and afterward received 10 ml of 0.9% saline injected into the femoral artery under sterile precautions. At 12 weeks, the patients received 0.5 ml distilled water as a placebo injection subcutaneously for 5 days followed by an IV 0.9% 5 ml saline injection on the sixth day. All participants were asked to monitor a five-point glucose profile using a glucometer at least once per week. Patients were also advised to perform physical activity in the form of a brisk walk for 150 min per week. The primary end point was a reduction in insulin requirement by ≥50% from baseline while maintaining HbA1c <7%. Study data suggests a reduction in exogenous insulin requirement while maintaining target HbA1c and an improvement in stimulated C-peptide response in patients with Type 2 DM. Study limitations include short-term follow-up only and small study population. Adverse events included splenic artery spasm, superior pancreaticoduodenal artery spasm, and celiac plexus spasm.

There is insufficient evidence to demonstrate improved outcomes with HSCT for the treatment of type 2 DM. Further, there is a lack of professional society support in the form of published consensus guidelines. The role of HSCT has not been established for this indication.

**The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative (2014):**
No relevant statements.

**Use Outside of the US**
British Society of Paediatric and Adolescent Rheumatology: Foster et al. (2006) published guidelines regarding the use of autologous HSCT for patients with severe rheumatic disease. The guidelines state that autologous HSCT can be used as a treatment option for children or young persons who have any subtype of JIA who fulfill certain inclusion/exclusion criteria based on severity of disease and persistent disease activity, failure of immunosuppressive and anti-inflammatory therapy, and drug toxicity or intolerance.

European Group for Blood and Marrow Transplantation (EGBMT): Snowden et al. (2011) published updated guidelines for the use of HSCT for the treatment of autoimmune diseases. The Guidelines note that autologous HSCT may be appropriate for carefully selected subpopulations of individuals with multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, Crohn’s disease, idiopathic thrombocytopenia purpura, autoimmune hemolytic anemia, thrombotic thrombocytopenic purpura, and juvenile idiopathic arthritis. Allogeneic HSCT may be considered for selected subpopulations with autoimmune cytopenia.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
   2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Experimental/Investigational/Unproven when used to report hematopoietic stem-cell transplantation for the treatment of autoimmune diseases and for the treatment of type 2 diabetes mellitus:

<table>
<thead>
<tr>
<th>CPT* Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Transplant preparation of hematopoietic progenitor cells; tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>Transplant preparation of hematopoietic progenitor cells; red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>Transplant preparation of hematopoietic progenitor cells; platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, oruffy coat layer</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem cell transplantation, allogeneic</td>
</tr>
</tbody>
</table>
| S2150       | Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including:
pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition


References


