Name of Policy:
Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

Policy #: 485       Latest Review Date: October 2014
Category: Surgery       Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Most patients with autoimmune disorders respond to conventional therapies. 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 stem-cell transplantation (HSCT).

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 chronic immune demyelinating polyneuropathy (CIDP). The National Institutes of Health (NIH) estimates 5 to 8% of Americans have an autoimmune disorder.

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

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 stem-cell transplantation (HSCT). HSCT 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.

Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation (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 stem cells may be obtained from the transplant recipient (autologous HSCT) or from a donor (allogeneic HSCT). 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). Cord blood is discussed in greater detail in medical policy #439 Placental/Umbilical Cord Blood as a Source of Stem Cells.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).
Autologous Stem-Cell Transplantation for Autoimmune Diseases
The goal of autologous HSCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablative) and generate new self-tolerant lymphocytes. This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablative), as is often performed in autologous HSCT for hematologic malignancies. However, there is currently no standard conditioning regimen for autoimmune diseases and both lymphoablative and myeloablative regimens are used. The efficacy of the different conditioning regimens has not been compared in clinical trials.

Currently, for autoimmune diseases, autologous transplant is preferred over allogeneic, in part because of the lower toxicity of autotransplant relative to allogeneic, the GVHD associated with allogeneic transplant, and the need to administer post-transplant immunosuppression after an allogeneic transplant.

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

Policy:
Autologous or allogeneic hematopoietic stem-cell transplantation does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational as a treatment of autoimmune diseases, including, but not limited to multiple sclerosis, juvenile idiopathic and rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis/scleroderma, Type I diabetes mellitus, and chronic inflammatory demyelinating polyneuropathy.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
The most recent literature review was performed through September 15, 2014. Recent reviews summarize the experience to date with hematopoietic stem-cell transplantation (HSCT) and autoimmune diseases.
As of March 2009, patients with an autoimmune disease registered in the European Group for Blood and Marrow Transplantation/European League Against Rheumatism (EBMT/EULAR) database who have undergone HSCT include a total of 1,031 with the clinical indications of multiple sclerosis (MS) (n=379), systemic sclerosis (n=207), systemic lupus erythematosus (SLE) (n=92), rheumatoid arthritis (RA) (n=88), juvenile idiopathic arthritis (n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn’s disease (n=23).

**Multiple Sclerosis**

Multiple sclerosis (MS) is the most common autoimmune disease for which autologous HSCT is being studied. Following initial promising clinical experience, more than 350 consecutive cases have been reported by the EBMT over the last decade. Most patients who underwent autologous HSCT for MS in the early studies had secondary progressive MS, and relatively fewer had relapsing remitting disease, with a Kurtzke Expanded Disability Status Scale (EDSS) of 3.0–9.5 at the time of HSCT. Improvements in supportive care and patient selection have contributed to improved outcomes, with a significant reduction in treatment-related mortality to 1.3% seen during 2001 to 2007. It is now generally accepted that administering HSCT relatively early in the course of the disease to reduce inflammation before irreversible neuronal damage occurs is important. Current studies target MS patients with active disease and worsening disability, as evidenced clinically by relapse, change in EDSS, and/or inflammatory activity seen on magnetic resonance imaging (MRI) and who have failed at least one approved first-line immunomodulatory MS therapy for enrollment. Follow-up of several years will be needed to evaluate outcomes of these clinical trials.

A 2011 systematic review evaluated the safety and efficacy of autologous HSCT in patients with progressive MS refractory to conventional medical treatment. Eight case series were included which met the inclusion criteria for the primary outcome of progression-free survival (PFS) with a median follow-up of at least two years. An additional six studies were included for a summary of mortality and morbidity. For the eight case series, there was substantial heterogeneity across studies. 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 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 2010 review summarizes the experience with HSCT and MS. A small number of patients have undergone autologous HSCT for the rare malignant form of MS, which is characterized by very active inflammatory disease with high relapse rates leading to a rapid progression of disabilities from the onset. These patients had persistent disease activity despite numerous different treatments. All patients but one were relapse-free without the need for ongoing
immunosuppression after autologous HSCT with up to 66 months of follow-up. One patient experienced a mild relapse that improved with conventional treatment. All of the patients had remarkable improvement in their functional abilities.

The majority of patients who have undergone autologous HSCT have had poor prognosis MS, which manifests as frequent relapses or the early onset of the secondary progressive (SPMS) phase of the illness within three to five years of diagnosis. Studies are mainly case series that report the outcomes of autologous HSCT in MS patients with ongoing disease activity that is refractory to conventional disease-modifying agents. There has not been a “standard” transplant regimen, and different mobilization and conditioning regimens have been used throughout the published series. Clinical relapses were reported following autologous HSCT in one series, but overall, there has been an absence of ongoing acute episodic inflammatory disease activity in most reports. Evidence of ongoing chronic disease activity was seen in 14 to 76% of cases in the different series, with median follow-up between 1.5 to three years. Although the frequency of progression seems to be similar to what might be expected from historical controls, in many of the transplant studies, between 5% and 60% of patients actually had significant and sustained improvement in their disability score, and MS PFS seems to level off with increasing length of follow-up after autologous HSCT, a change from the expected natural history of progressive disabilities increasing with time.

Burt et al have transplanted 21 patients with relapsing-remitting MS with ongoing relapses during treatment with interferon. 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 score.

The EBMT Autoimmune Diseases Working Party database reported new data from a retrospective survey of 178 patients with MS who underwent autologous HSCT following one of several different preparative regimens. Overall, at median follow-up of about 42 months, the disease remained stable or improved in 63% of cases and worsened in 37%. Autologous HSCT was associated with significantly better PFS in a subset of younger patients (i.e., younger than 40 years of age) affected by severe, progressive MS who received autologous HSCT within five years from diagnosis compared to those older than 40 years. The authors suggest that autologous HSCT could be considered after failure of conventional treatments in patients with rapidly progressing MS.

Fassas and colleagues in 2011 reported the long-term results of a Phase I/II study conducted in a single center which investigated the effect of HSCT in the treatment of MS. 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 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 one) 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.

Schevchenko and colleagues in 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. 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 magnetic resonance imaging 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).

Mancardi and colleagues in 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. Clinical and magnetic resonance imaging outcomes were reported. The median follow-up period was 48.3 months (range = 0.8 to 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 to 12 months confirmed. Expanded Disability Status Scale improvement >1 pint 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, with (44%) remained stable or had a sustained improvement while ten (56%), after an initial period of stabilization or improvement with a median duration of 3.5 years, showed a slow disability progression.

Bowen and colleagues in 2012 reported the long-term safety and effectiveness of high-dose immunosuppressive therapy followed by autologous HSCT in advanced MS. Neurological examinations, brain magnetic resonance imaging and cerebrospinal fluid (CSF) for oligoclonal bands (OCB) were serially evaluated. There were 26 patients with a mean Expanded Disability Status Scale (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% confidence interval, 0.30 to 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 neurological worsening after treatment. HSCT may be more effective in patients with less advanced relapsing/remitting MS.
Systemic Sclerosis/Scleroderma
A recent review article summarizes the clinical studies that have been performed using conventional therapy, as well as those using autologous HSCT in the treatment of systemic sclerosis. Ongoing randomized trials are also discussed.

The results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published in June 2014. ASTIS was a Phase III randomized controlled trial (RCT) conducted in ten 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 200mg/kg over four consecutive days and intravenous rabbit antithymocyte globulin 7.5mg/kg total dose over three consecutive days) followed by CD34+ selected autologous HSCT support (n=79) or 12 monthly treatments with intravenous pulsed cyclophosphamide (750mg/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. 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 fatal 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 nonadherence. Furthermore, the article states that crossover was allowed 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.

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% in 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).

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 cyclophosphamide. Nineteen consecutively enrolled patients who were younger than 60 years of age with diffuse systemic sclerosis, modified Rodnan skin scores (mRSS) of more than 14, and internal organ involvement or restricted skin involvement (mRSS <14) but coexistent pulmonary involvement were randomly allocated 1:1 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 ten 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 eleven 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.

Vonk et al reported the long-term results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HSCT from 1998 to 2004. 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 years), 81% (n=21 of 26) of the patients demonstrated a clinically beneficial response. Skin sclerosis was measured with a modified Rodnan skin score, and a significant (i.e., greater than 25%) decrease (i.e., improvement) was achieved in 19 of 26 patients after one year and in 15 of 16 after five years. At inclusion into the study, 65% of patients had significant lung involvement; all pulmonary function parameters remained stable after transplant at five and seven years’ follow-up. Analyzing World Health Organization (WHO) performance status, which reflects the effect of HSCT on the combination of functional status, skin, lung, heart, and kidney involvement, the percentage of patients with a performance score of 0 increased to 56% compared to 4% at baseline. Estimated survival at five years was 96.2% (95% CI 89 to 100%) and at seven years was 84.8% (95% CI 70.2 to 100%) and event-free survival, (survival without mortality, relapse, or progression of systemic sclerosis resulting in major organ dysfunction) was 64.3% (95% CI 47.9 to 86%) at five years and 57.1%
(95% CI 39.3 to 83%) at seven years. For comparison, an international meta-analysis published in 2005 estimated the five-year mortality rate in patients with severe systemic sclerosis at 40%.

Nash et al 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. Of the 34 patients, 79% survived one year and were evaluable for response (there were eight transplant-related deaths and four systemic sclerosis-related deaths). Seventeen of the 27 (63%) evaluable patients had sustained responses at a median follow-up of four years (range, 1 to 8 years). Skin biopsies showed a statistically significant decrease in dermal fibrosis compared with baseline (p<0.001) and, in general, lung, heart, and kidney function remained stable. Overall function as assessed in 25 patients by the modified Health Assessment Questionnaire Disability Index showed improvement in 19, and disease response was observed in the skin of 23 of 25 and lungs of eight of 27 patients. Estimated overall and PFS were both 64% at five years.

Henes and colleagues in 2012 reported on their experience with autologous HSCT for systemic sclerosis in 26 consecutive patients scheduled for HSCT between 1997 and 2009. 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 even after month six. Three patients died between mobilization and condition 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.

Systemic Lupus Erythematosus

Burt et al published the results of the largest single-center series of this treatment in systemic lupus erythematosus (SLE) available in the U.S. Between April 1997 through January 2005, they enrolled 50 patients (mean age: 30 years [SD +/- 10.9 years], 43 women, seven men) with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement in a single-arm trial. All subjects had at least four of eleven American College of Rheumatology criteria for SLE and required more than 20mg per day of prednisone or its equivalent in spite of use of cyclophosphamide. Patients underwent autologous SCT following a lymphoablative conditioning regimen. Two patients died after mobilization, yielding a treatment-related mortality of 4% (2/50). After a mean follow-up of 29 months (range, six months to 7.5 years), overall five-year survival was 84%, and the probability of disease-free survival was 50%. Several parameters of SLE activity (described in the 2001 TEC Assessment [4]) improved, including renal function, SLE disease activity index (DAI) score, antinuclear antibody, anti-ds DNA, complement, and carbon monoxide diffusion lung capacity. The investigators suggest these results justify a randomized trial comparing immunosuppression plus autologous SCT versus continued standard of care.
Song and colleagues in 2011 reported on the efficacy and toxicity of autologous stem cell transplantation for 17 patients with SLE after seven years follow-up. The probabilities of OS and PFS were used to assess the efficacy and toxicities of the treatment. The median follow-up time was 89 months (range 33-110 months). The probabilities of seven-year OS and PFS were 82.4% ± 9.2% and 64.7% ± 11.6%, respectively. The principal adverse events included allergy, infection, elevation of liver enzymes, bone pain, and heart failure. Two patients died due to severe pneumonia and heart failure at 33 and 64 months after transplantation, respectively. The authors concluded that their seven-year follow-up results suggest that autologous HSCT seems beneficial for SLE patients.

**Juvenile Arthritis**

A review article by Saccardi et al summarizes the experience thus far with juvenile idiopathic and rheumatoid arthritis (RA) as follows: 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. The frequency of HSCT for RA 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.

**Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)**

Several review articles have summarized experience with HSCT in treatment of CIDP. In general, evidence comprises a few case reports describing outcomes of autologous HSCT in patients who failed standard treatments such as corticosteroids, intravenous immunoglobulins, and plasma exchange.

**Type I Diabetes Mellitus**

Couri et al reported the results of a prospective Phase I/II study of autologous HSCT in 23 patients with Type 1 diabetes mellitus (age range, 13 to 31 years) diagnosed in the previous six weeks by clinical findings with hyperglycemia and confirmed by measurement of serum levels of antiglutamic acid decarboxylase antibodies. Enrollment was November 2003 to April 2008, with follow-up until December 2008. After a mean follow-up of 29.8 months (range, 7-58 months) following autologous nonmyeloablative HSCT, C-peptide levels increased significantly (C-peptide is a measure of islet cell mass, and an increase after HSCT indicates preservation of islet cells), and the majority of patients achieved insulin independence with good glycemic control. Twenty patients without previous ketoacidosis and not receiving corticosteroids during the preparative regimen became insulin-free. Twelve patients maintained insulin independence for a mean of 31 months (range, 14 to 52 months), and eight patients relapsed and resumed low-dose insulin. In the continuously insulin-independent group, HbA1c levels were less than 7.0% and mean area under the curve (AUC) C-peptide levels increased significantly from 225.0 (standard error [SE], 75.2) ng/mL per two hours pre-transplantation to 785.4 (SE, 90.3) ng/mL per two hours at 24 months post-transplantation (p=0.001) and to 728.1 (SE 144.4) ng/mL per two hours at 36 months (p=0.001). In the transiently insulin-independent group, mean AUC of C-peptide levels also increased from 148.9 (SE 75.2) ng/mL per two hours pre-transplantation to 546.8 (SE 96.9) ng/mL per two hours at 36 months (p=0.001), which was sustained at 48 months. In this latter group, two patients regained insulin independence after treatment with
sitagliptin (Januvia®), which was associated with an increase in C-peptide levels. There was no transplant-related mortality.

**Other Autoimmune Diseases**
Phase II/III protocols are being developed for Crohn’s disease and chronic inflammatory demyelinating polyneuropathy. For the remaining autoimmune diseases (including immune cytopenias, relapsing polychondritis, and others), the numbers are too small to draw conclusions, with further Phase I/II pilot studies proceeding.

**Summary**
Initial studies focused on using hematopoietic stem-cell transplantation (HSCT) as salvage therapy for end-stage treatment of refractory autoimmune diseases. More recent experience has better helped to define which patients are most likely to benefit from HSCT, and the field has shifted to the use of HSCT earlier in the disease course before irreversible organ damage and to the use of safer and less intense nonmyeloablative conditioning regimens.

The experience with HSCT and autoimmune disorders has been predominantly with autologous transplants, and a number of published clinical reports with follow-up have demonstrated the safety and in some patients (particularly those with systemic sclerosis, SLE, and MS) the impact of HSCT in selected autoimmune diseases.

The results of the ASTIS trial suggest high-dose chemotherapy with autologous HSCT may improve survival among patients with diffuse cutaneous systemic sclerosis compared with pulsed intravenous cyclophosphamide. However, analysis of the internal validity of the trial using USPSTF criteria showed fatal flaws and a poor study rating due to attrition in the control group that could have skewed the survival curve to show better survival for HSCT recipients compared with controls. The investigators acknowledge this limitation in addition to stating that the unblinded outcome assessments may have influenced results, and wide confidence intervals for some secondary outcomes indicated less certainty about those results. An accompanying editorial concurs that autologous HSCT to treat systemic sclerosis requires further study before it should be offered to patients in routine clinical practice.

Although some of the initial results have been promising, this field continues to evolve. Many trials (randomized and nonrandomized) are currently recruiting or ongoing comparing the use of HSCT to conventional therapy for most of the diseases addressed in this policy; the results of these trials will further define the role of HSCT in the management of these diseases. Thus, use of HSCT for these autoimmune diseases is considered investigational.

**Practice Guidelines and Position Statements**
A review of the guidelines from the American Academy of Neurology and the American College of Rheumatology did not find the mention of stem-cell transplantation in guidelines for MS, lupus, RA, or juvenile arthritis. No pertinent guidelines for autologous stem-cell transplantation for autoimmune diseases were identified.

**U.S. Preventive Services Task Force Recommendations**
Stem cell transplantation is not a preventive service.
**Key Words:**
Autoimmune Diseases, High-Dose Chemotherapy/Stem-Cell Rescue, High-Dose Chemotherapy, Autologous Stem Cell Transplant, Multiple Sclerosis, Rheumatoid Arthritis, Systemic Sclerosis/Scleroderma, Systemic Lupus Erythematosus (SLE), Juvenile Arthritis, Type I Diabetes Mellitus

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Coding:**
CPT Codes:

- **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
- **38208**  Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing per donor
- **38209**  ;thawing of previously frozen harvest, with washing per donor
- **38210**  ;specific cell depletion with harvest, T-cell depletion
- **38211**  ;tumor-cell depletion
- **38212**  ;red blood cell removal
- **38213**  ;platelet depletion
- **38214**  ;plasma (volume) depletion
- **38215**  ;cell concentration in plasma, mononuclear, or buffy coat layer
- **38220**  Bone marrow; aspiration only
- **38221**  ;biopsy, needle or trocar
- **38230**  Bone marrow harvesting for transplantation; allogeneic
- **38232**  ; autologous *(Effective for dates of service on or after January 1, 2012)*
- **38240**  Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
- **38241**  ;autologous

HCPCS
- **Q0083–Q0085**  Chemotherapy administration code range
- **J9000–J9999**  Chemotherapy drugs code range
S2150 Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic, and emergency services)

References:


Policy History:
Medical Policy Group, September 2011
Medical Policy Administration Committee, October, 2011
Available for comment October 5 through November 21, 2011
Medical Policy Group, December 2011 (3): Updated CPT Codes 38208 & 38209 and added code 38230 & 38232 for 2012 code updates
Medical Policy Group, October 2012 (3): 2012 Updates to Key Points, Key Words and References
Medical Policy Panel, October 2013
Medical Policy Group, October 2013 (3): 2013 Updates to Description, Key Points and References; policy statement added chronic inflammatory demyelinating polyneuropathy to included but not limited to list of autoimmune diseases for which this treatment is considered investigational
Available for comment October 16 through November 30, 2013
Medical Policy Panel, October 2014
Medical Policy Group, October 2014 (3): 2014 Updates to Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.