Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

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Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers autologous or allogeneic hematopoietic stem-cell transplantation (HSCT) as a treatment of autoimmune diseases, including, but not limited to multiple sclerosis (MS), juvenile idiopathic arthritis (JIA), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma, type 1 diabetes mellitus, and chronic inflammatory demyelinating polyneuropathy (CIDP) to be investigational.*

Background/Overview
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 HSCT.

Autoimmune Diseases
Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including MS, RA, SLE, systemic sclerosis/scleroderma, and CIDP. The National Institutes of Health (NIH) estimates that 5–8% 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 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 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
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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 “naive” and thus, are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous 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 (lymphoaualtion) and generate new self-tolerant lymphocytes. This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablation), as is often performed in autologous HSCT for hematologic malignancies. However, there is currently no standard conditioning regimen for autoimmune diseases and both lymphoaualtive and myeloablation 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.

Rationale/Source
Two TEC Assessments have addressed the issue of high-dose lymphoaualtive therapy and stem-cell rescue in autoimmune diseases and support the policy.

Recent reviews summarize the experience to date with 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 MS (n=379), systemic sclerosis (n=207), SLE (n=92), RA (n=88), juvenile idiopathic arthritis (n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn’s disease (n=23).
Multiple Sclerosis
Currently, 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 2001–2007. 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 systematic review published in 2011 evaluated the safety and efficacy of autologous HSCT in patients with progressive MS refractory to conventional medical treatment. Eight case series were included that met the inclusion criteria for the primary outcome of progression-free survival (PFS) with a median follow-up of at least 2 years. An additional 6 studies were included for a summary of mortality and morbidity. For the 8 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 5 studies using an intermediate-intensity regimen, while the other 3 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 7 treatment-related deaths were recorded; 6 non-treatment-related deaths occurred, 5 associated with disease progression.

A review published in 2010 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 3 to 5 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
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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 14–76% of cases in the different series, with median follow-up between 1.5 to 3 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 and colleagues 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 1-point or greater improvement in their EDSS scores.

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 5 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 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. 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 2 years (0-6). Improvements by 0.5-5.5 (median 1) EDSS points were observed in 16 cases lasting for a median of 2 years. In 9 of these patients, EDSS scores did not progress above baseline scores. Two patients died, at 2 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 and colleagues 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 5 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).

Mancardi and colleagues 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 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 5 years, 66% of patients remained stable or improved. Among patients with a follow-up longer than 1 year, 8 out of 25 subjects with a relapsing-remitting course (31%) had a 6-12 months confirmed Expanded Disability Status Scale improvement >1 point after HSCT, as compared with 1 out of 36 (3%) patients with a secondary progressive disease course (p=0.009). Among the 18 cases with a follow-up longer than 7 years, 8 (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 and colleagues reported the long-term safety and effectiveness of high-dose immunosuppressive therapy followed by autologous HSCT in advanced MS. 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, 8 with primary progressive, and 1 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; 4 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 7 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.

Clinical Trials
A Phase III randomized trial (Stem Cell Therapy for Patients With Multiple Sclerosis Failing Interferon A Randomized Study) is recruiting participants to study the effect of autologous peripheral blood HSCT in patients with relapsing MS versus U.S. Food and Drug Administration (FDA)-approved standard of care. Primary endpoint is disease progression. Patients will be followed for 5 years after randomization. Estimated enrollment is 110, and estimated study completion date is January 2013 (NCT00273364).

The Phase II randomized ASTIMS trial evaluating autologous HSCT in severe cases of MS was terminated due to difficulty in accruing patients and lack of funds.

The High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) Study is a Phase II nonrandomized, uncontrolled trial to determine the effectiveness of autologous HSCT for the treatment of poor prognosis (relapsing-remitting or secondary progressive) MS. The primary
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outcome measure is time to treatment failure. Estimated enrollment is 25, and estimated study completion date is September 2015 (NCT00288626).

The Canadian MS-BMT Phase II study is to determine the effect of autologous HSCT on early-stage MS. Estimated enrollment is 24. Enrollment completed July 2009.

Systemic Sclerosis/Scleroderma

A review published in 2011 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.

An open-label, randomized, controlled Phase 2 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 6 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 9 allocated to cyclophosphamide (p=0.00001). Treatment failure (i.e., disease progression without interval improvement), occurred in 8 of 9 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 2 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 1 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 2 years after HSCT suggested that the improvements in mRSS (p<0.0001) and forced vital capacity (p<0.03) persisted.

Vonk and colleagues reported the long-term results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HSCT from 1998 to 2004. There was 1 transplant-related death and 1 death due to progressive disease, leaving 26 patients for evaluation. After a median follow-up of 5.3 years (range, 1–7.5 years), 81% (n=21/26) of the patients demonstrated a clinically beneficial response. Skin sclerosis was measured with a modified Rodnan skin score, and a significant (i.e., greater than 25%) decrease (i.e., improvement) was achieved in 19 of 26 patients after 1 year and in 15/16 after 5 years. At inclusion into the study, 65% of patients had significant lung involvement; all pulmonary function parameters remained stable after transplant at 5 and 7 years’ follow-up. Analyzing World Health Organization (WHO)
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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 5 years was 96.2% (95% CI: 89-100%) and at 7 years was 84.8% (95% CI: 70.2-100%), and event-free survival, (survival without mortality, relapse, or progression of systemic sclerosis resulting in major organ dysfunction) was 64.3% (95% CI: 47.9-86%) at 5 years and 57.1% (95% CI: 39.3-83%) at 7 years. For comparison, an international meta-analysis published in 2005 estimated the 5-year mortality rate in patients with severe systemic sclerosis at 40%.

Nash and colleagues 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 1 year and were evaluable for response (there were 8 transplant-related deaths and 4 systemic sclerosis-related deaths). Seventeen of the 27 (63%) evaluable patients had sustained responses at a median follow-up of 4 years (range, 1-8 years). Skin biopsies showed a statistically significant decrease in dermal fibrosis compared with baseline (p<0.001) and, in general, lung, heart, and kidney function remained stable. Overall function as assessed in 25 patients 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 8 of 27 patients. Estimated overall survival (OS) and PFS were both 64% at 5 years.

Henes and colleagues 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 mRSS by 25%) at 6 months. Secondary endpoints were transplant-related mortality and PFS. At 6 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 6. Three patients died between mobilization and conditioning treatment, 2 due to severe disease progression and 1 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.

Clinical Trials
ASTIS is a Phase III randomized, international, multicenter trial. Patients with diffuse systemic sclerosis were randomized to high-dose immunoablation and autologous HSCT or pulsed cyclophosphamide. Crossover to the HSCT arm was not allowed. Outcome measures included survival and prevention of major organ failure, safety, and quality of life. As of 2009, enrollment was completed with 156 patients. Initial results were presented at EULAR 2012, the Annual Congress of the European League Against Rheumatism: as of May 1, 2012, data indicated that HSCT resulted in better long-term survival than conventional treatment for patients with poor prognosis early diffuse cutaneous systemic sclerosis.

The SCOT trial is a randomized Phase II study comparing HSCT and pulsed cyclophosphamide. Primary outcome measure is the global rank composite score at 54 months post-randomization (which includes measures of event-free survival, death, lung function, and skin score). Crossover to the HSCT arm is not
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allowed. The trial is still recruiting, with an estimated enrollment of 114 patients with an estimated study completion date of June 2016 (NCT00114530).

As of September 2013, neither ASTIS nor SCOT has been published in full-length form.

**Systemic Lupus Erythematosus**

Burt and colleagues published the results of the largest single-center series of this treatment in 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, 7 men) with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement in a single-arm trial. All subjects had at least 4 of 11 American College of Rheumatology criteria for SLE and required more than 20 mg 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, 6 months to 7.5 years), overall 5-year survival was 84%, and the probability of disease-free survival was 50%. Several parameters of SLE activity (described in the 2001 TEC Assessment) 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 reported on the efficacy and toxicity of autologous stem-cell transplantation for 17 patients with SLE after 7 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 7-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 7-year follow-up results suggest that autologous HSCT seems beneficial for SLE patients.

**Clinical Trials**

Three nonrandomized, open-label Phase II trials are recruiting patients, ongoing or completed studying the effectiveness of autologous HSCT in patients with SLE: one with an estimated enrollment of 9 and study completion date of April 2018 (NCT00076752), another with an estimated enrollment of 30 and study completion date of April 2014 (NCT00750971), and a third with an estimated enrollment of 52 and study completion date of April 2012 (NCT00271934).

**Juvenile Arthritis**

A review article by Saccardi et al. summarizes the experience thus far with juvenile idiopathic and 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 6 months of transplant.

Clinical Trials
No Phase II or III clinical trials were identified at online site: ClinicalTrials.gov using HSCT in juvenile idiopathic or RA.

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.

Clinical Trials
One non-randomized, Phase II clinical trial is recruiting patients to study nonmyeloablative autologous HSCT in patients with CIDP (NCT00278629). It is estimated the study will be complete in December 2014.

Type 1 Diabetes Mellitus
Couri and colleagues reported the results of a prospective Phase I/II study of autologous HSCT in 23 patients with type 1 diabetes mellitus (age range, 13-31 years) diagnosed in the previous 6 weeks by clinical findings with hyperglycemia and confirmed by measurement of serum levels of antiglutamic acid decarboxylase antibodies. Enrollment was November 2003-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, 14-52 months), and 8 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 2 hours pretransplantation to 785.4 (SE: 90.3) ng/mL per 2 hours at 24 months post-transplantation (p<0.001) and to 728.1 (SE: 144.4) ng/mL per 2 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 2 hours pretransplantation to 546.8 (SE: 96.9) ng/mL per 2 hours at 36 months (p=0.001), which was sustained at 48 months. In this latter group, 2 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.

Clinical Trials
Three Phase I/II and two Phase II trials are recruiting patients with type 1 diabetes mellitus for autologous HSCT (NCT00315133, NCT01121029, NCT00807651, NCT01341899, NCT1285934). The status of one Phase II and one Phase II/III trial for patients with type 2 diabetes mellitus for autologous HSCT is unknown. (NCT00644241, NCT01065298).
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Other Autoimmune Diseases
Phase II/III protocols are being developed for Crohn’s disease. 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 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.

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.

References
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose lymphoablative therapy (HDLT) with or without stem cell rescue for treatment of severe autoimmune diseases. TEC Assessments 2000; Vol 15, Tab 1.
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose lymphoablative therapy (HDLT) with or without stem-cell rescue for treatment of severe autoimmune diseases. TEC Assessments 2001; Vol 16, Tab 14.
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Policy History

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<td>Managed Care Advisory Council approval</td>
</tr>
<tr>
<td>06/24/2002</td>
<td>Format revision. No substance change to policy.</td>
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<tr>
<td>05/07/2004</td>
<td>Medical Director review</td>
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<td>05/18/2004</td>
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<td>06/28/2004</td>
<td>Managed Care Advisory Council approval. Format revision. No substance change to policy.</td>
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<tr>
<td>06/07/2006</td>
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<td>08/06/2008</td>
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<tr>
<td>08/20/2008</td>
<td>Medical Policy Committee approval. No change to coverage eligibility.</td>
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<td>08/06/2009</td>
<td>Medical Policy Committee approval</td>
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<tr>
<td>08/26/2009</td>
<td>Medical Policy Implementation Committee approval. No change to coverage eligibility. Title changed.</td>
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<tr>
<td>07/01/2010</td>
<td>Medical Policy Committee approval</td>
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<tr>
<td>07/21/2010</td>
<td>Medical Policy Implementation Committee approval. No change to coverage eligibility.</td>
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<tr>
<td>07/07/2011</td>
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<tr>
<td>07/20/2011</td>
<td>Medical Policy Implementation Committee approval. Added indications of juvenile idiopathic arthritis and diabetes mellitus to policy statement as investigational.</td>
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<td>06/28/2012</td>
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<td>07/27/2012</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
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<tr>
<td>03/04/2013</td>
<td>Coding update</td>
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<tr>
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<td>08/21/2013</td>
<td>Medical Policy Implementation Committee approval. Coverage eligibility unchanged.</td>
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<tr>
<td>09/04/2014</td>
<td>Medical Policy Committee review</td>
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Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

Policy # 00050
Original Effective Date: 01/28/2002
Current Effective Date: 09/17/2014

09/17/2014 Medical Policy Implementation Committee approval. Chronic inflammatory demyelinating polyneuropathy added as investigational.

Next Scheduled Review Date: 09/2015

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

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