



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Stem-Cell Transplantation for Autoimmune Diseases

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INSTRUCTIONS FOR USE

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Coverage Policy

CIGNA does not cover hematopoietic stem-cell transplantation (HSCT) for the treatment of an autoimmune disease, including ANY of the following, because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- 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
-

General Background

Autoimmune diseases are a group of highly heterogeneous disorders with variable organ system involvement, diverse etiologies and pathologies, and different prognoses (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.

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).

HSCT has been proposed for the treatment of a number of autoimmune diseases including, but not limited to, multiple sclerosis (MS), rheumatoid arthritis (RA), systemic sclerosis, also known as scleroderma (Ssc), systemic lupus erythematosus (SLE), and juvenile idiopathic arthritis (JIA), gastrointestinal autoimmune diseases such as Crohn's disease, celiac disease, and ulcerative colitis, type I diabetes mellitus, autoimmune hepatitis, cryptogenic cirrhosis, immune vasculitis, dermatomyositis, polymyositis, and neuromyelitis optica. It has also been proposed for immune cytopenias such as autoimmune hemolytic anemia, and thrombotic thrombocytopenia purpura, among others.

The intense immunosuppression used with HSCT, which approaches or exceeds the myeloablative level, is thought to eliminate T cells causing 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). The goal is to generate new self-tolerant lymphocytes with lymphoablation rather than to ablate and reconstitute the entire hematopoietic system (i.e., myeloablation) (Burt, 2006).

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). Conditioning regimens used with allogeneic HSCT are designed to suppress the recipient immune response while causing minimal toxicity and may be myeloablative or nonmyeloablative (i.e., lympho/immunoablative).

The occurrence of new autoimmune phenomena has been described after allogeneic or autologous HSCT, including the production of autoantibodies and, more rarely, autoimmune thyroid disease and cytopenias. The underlying mechanisms are not well understood, but graft-versus-host disease and homeostatic expansion following transplant-induced lymphopenia has been implicated (Nikolov, 2008).

The effectiveness of myeloablative or lymphoablative conditioning and HSCT remains unclear. HSCT may potentially induce remissions in subsets of patients with autoimmune disorders refractory to conventional therapy; however, 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. The peer-reviewed, published scientific research includes retrospective analyses, small case studies, feasibility studies, and phase I/II trials; however, phase III clinical trials are ongoing. Transplant-related toxicity is a known risk for morbidity and mortality. Although results of published studies are promising, in the absence of outcomes from well-designed randomized controlled trials the role of HSCT for any autoimmune disease has not yet been established.

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. Multi-center clinical trials will need to be conducted (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 (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.

In a study by Gratwohl (2005) based on a retrospective review of data from the European Group for Blood and Marrow Transplantation (EBMT) Autoimmune Working Party Database involving autologous HSCT for various autoimmune disorders, varied conditioning regimens were used and grouped into the categories of high- (17%), intermediate- (52%) and low-intensity (31%) conditioning. Treatment response was noted in 81% with a sustained response in 71%. Disease progression was 49% at three years, despite initial response. At a median follow-up of 20 months, three-year overall survival (OS) was 89%. Overall mortality was 11%; 58% of deaths were of transplantation-related causes.

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.

Additional clinical studies investigating specific autoimmune diseases include but are not limited to, the following:

Juvenile Idiopathic Arthritis (JIA): Brinkman et al. (2007) reported on a cohort of 22 children with refractory, progressive JIA who underwent HSCT after pretreatment with intensive immunosuppression in a multicenter, phase II clinical trial. Eighteen patients had systemic JIA and four patients had polyarticular JIA. After a median follow-up of 80 months, 68% of patients achieved a sustained remission or significant improvement. TRM 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%.

A multi-center retrospective analysis of 34 pediatric patients with refractory JIA was performed by Wulffraat et al. (2005) Fifty-three percent of patients with a follow-up of 12–60 months achieved a drug-free complete remission; however, there was 9% treatment-related mortality (TRM) and 6% disease-related mortality.

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): A number of retrospective analyses, case series, and phase I/II trials have been published regarding the safety and effectiveness of autologous HSCT for MS. In several studies improvement in the Expanded Disability Scale Scores following transplantation was reported for a majority of patients (Burt, 2009; Fagius, 2009; Shevchenko, 2008; Portaccio, 2007; Saccardi, 2006; Ni, 2006; Su, 2006).

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%.

Burt et al. (2009) 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.

Fagius et al. (2009) performed autologous hematopoietic stem-cell transplantation (HSCT) in nine patients with malignant relapsing-remitting MS. Median follow-up time was 29 months, which was longer than the median duration of MS prior to transplantation. Median expanded disability status scale (EDSS) prior to transplantation was 7.0; after transplantation there was median improvement of 3.5 steps on the scale. Before transplantation, there were 62 relapses per 82 patient months. Post transplantation there was one relapse in 289 patient months. Although results are promising, this study is limited by small size, lack of randomization, and short follow-up.

Shevchenko et al. (2008) retrospectively evaluated the outcomes of 50 patients with various subtypes of MS (i.e., primary progressive, secondary progressive, relapsing-remitting, progressive relapsing) who underwent high dose immunosuppressive therapy and autologous HSCT. As compared with the baseline, approximately sixty-two percent improved by at least 0.5 points on the EDSS. Results of magnetic resonance imaging (MRI) scans were available for 37 patients. Forty-three percent had active lesions at baseline; after transplantation all were inactive except two. Of the 21 patients without active lesions at baseline, all remained inactive except one that showed active disease after transplantation. No new, active lesions were registered in patients who were without disease progression. Overall progression-free survival (PFS) was 72%. All patients who did not have progression of disease were off therapy throughout the post-transplantation period. Limitations to the study included a lack of randomization, variability in selection criteria, short follow-up, and small participant numbers.

On behalf of the European Group for Blood and Marrow Transplantation (EBMT), Saccardi et al. (2006) reported the results of a retrospective analysis of 178 individuals with various types of MS who received an autologous HSCT. Early non-neurological toxicity was reported in 56% of patients. Overall TRM was 5.3%. Overall survival (OS) at eight years was 91.2%. The patient's disability status decreased or remained stable in 63% of patients and worsened in 37% of patients. This study is limited by a lack of randomization and the heterogeneity of participant diagnosis (i.e., varying subtypes/degrees of MS).

Although results of published studies are promising, varying patient eligibility criteria, lack of randomization, and nonstandard immunosuppressive treatment regimens limit the ability to determine the safety and effectiveness of HSCT for the treatment of MS. At this time the role of HSCT has not yet been established for this indication.

Rheumatoid Arthritis (RA): Verburg and colleagues (2005) reported on the outcomes of eight patients with active, refractory, progressively erosive RA who received high-dose chemotherapy and autologous HSCT. Assessment showed a decreased progression of joint damage after transplantation per the Larsen score.

Data are lacking in the published peer-reviewed scientific literature to determine safety and effectiveness of HSCT for the treatment of RA. The role of HSCT for this indication has not yet been established.

Systemic Lupus Erythematosus (SLE): Burt et al. (2006) studied 50 patients with refractory SLE enrolled in a single-arm trial. Two patients died after mobilization of cells but prior to transplant. By intention to treat analysis transplant-related mortality (TRM) was 4%. 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 SLE Disease Activity Index score, anti-nuclear antibody (ANA), antidouble strand deoxyribonucleic acid, complement, and carbon monoxide diffusion capacity. These data are nonrandomized and thus preliminary.

Although results of published reports are promising, lack of randomization and small participant populations limit the ability to determine safety and effectiveness of HSCT for the treatment of SLE. The role of HSCT for this indication has not yet been established.

Systemic Sclerosis (Ssc): 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 and small participant population.

Oyama et al. (2007) reported the outcomes of a phase I trial evaluating the use of nonmyeloablative conditioning and autologous HSCT in ten consecutive patients with poor prognosis Ssc. Treatment-related mortality (TRM) was zero. At a median follow-up of 25.5 months, nine out of ten patients were alive. There was a statistically significant improvement of the post-transplantation skin scores. Cardiac, pulmonary, and renal function remained stable without significant change. After median follow-up of 25.5 months, the overall survival (OS) and progression-free survival (PFS) rates were 90% and 70%, respectively.

Nash et al. (2007) reported the long-term follow-up results of a phase II, single-arm study of high-dose immunosuppressive therapy and autologous HSCT for 34 patients with diffuse cutaneous systemic sclerosis (Ssc). Seventeen of 27 evaluable patients who survived one year (63%) had sustained responses at a median of four years, including improvement in skin and overall function. Transplant-related mortality (TRM) was 23%, while disease-related death was 12%. Estimated progression-free survival (PFS) and OS at five years were 64%.

Although results are promising, there is insufficient evidence to support the safety and effectiveness of HSCT for the treatment of Ssc. The role of HSCT has not yet been established for this indication.

Professional Societies/Organizations

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.

Summary

Although results of several prospective and retrospective studies are promising, there is insufficient evidence supporting the safety or effectiveness of hematopoietic stem-cell transplantation (HSCT) for the treatment of any autoimmune disease. The role of this therapy has not yet been established for these indications.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Experimental/Investigational/Unproven/Not Covered when used to report hematopoietic stem-cell transplantation for the treatment of autoimmune diseases:

CPT* Codes	Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38241	Bone marrow or blood-derived peripheral stem cell transplantation; autologous
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

HCPCS Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic
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

ICD-9-CM Diagnosis Codes	Description
250.11	Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled
250.13	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled
250.21	Diabetes with hyperosmolarity, type 1 [juvenile type], not stated as uncontrolled
250.23	Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled
250.31	Diabetes with other coma, type I [juvenile type], not stated as uncontrolled
250.33	Diabetes with other coma, type I [juvenile type], uncontrolled
250.41	Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
250.43	Diabetes with renal manifestations, type I [juvenile type], uncontrolled
250.51	Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
250.53	Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
250.61	Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled
250.63	Diabetes with neurological manifestations, type I [juvenile type], uncontrolled

250.71	Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as uncontrolled
250.73	Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled
250.81	Diabetes mellitus with other specified manifestations, type I [juvenile type], not stated as uncontrolled
250.83	Diabetes mellitus with other specified manifestations, type I [juvenile type], uncontrolled
250.91	Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled
250.93	Diabetes with unspecified complication, type I [juvenile type], uncontrolled
283.0	Autoimmune hemolytic anemias
340	Multiple sclerosis
341.0	Neuromyelitis optica
446.6	Thrombotic microangiopathy
447.6	Arteritis, unspecified
555.0-555.9	Regional enteritis
556.0-556.9	Ulcerative colitis
571.42	Autoimmune hepatitis
571.5	Cirrhosis of liver without mention of alcohol
579.0	Celiac disease
710.0	Systemic lupus erythematosus
710.1	Systemic sclerosis
710.3	Dermatomyositis
710.4	Polymyositis
714.0-714.9	Rheumatoid arthritis and other inflammatory polyarthropathies

***Current Procedural Terminology (CPT®) © 2010 American Medical Association: Chicago, IL.**

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	6/15/2008	0357	Stem-Cell Transplant for Autoimmune Diseases

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