Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Autoimmune Diseases**

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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 indications, 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).

The goal of HSCT for autoimmune diseases is to generate self-tolerant lymphocytes with lymphoablation rather than to ablate and reconstitute the entire hematopoietic system (i.e., myeloablation) (Burt, 2006).The intense immunosuppression used with HSCT, which approaches or exceeds the myeloablative level, is thought to eliminate T-cells which cause the autoimmune response. It is also theorized that the regeneration of bone marrow with transplanted stem cells normalizes the immune system, possibly by the elimination of self-reactive lymphocytes from the patient and the creation of a tolerant immune system (Tyndall and Gratwohl, 2000).

Conditioning regimens used with allogeneic HSCT for autoimmune diseases are designed to suppress the recipient immune response while causing minimal toxicity and may be myeloablative or nonmyeloablative (i.e., lympho/immunoablative) in dosage. Very high doses of immunosuppressive chemotherapy may cause myelosuppression, necessitating rescue with transfused hematopoietic stem cells; most commonly, autologous cells are used. In some studies, treatment-related mortality (TRM) rates of individuals who have undergone autologous HSCT for autoimmune disorders have been noted to be higher than the rates in patients with non-autoimmune diseases; 5%–15% versus 1%–5%, respectively (Nikolov, 2008).

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

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

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

Snowden et al. (2011) retrospectively analyzed outcomes of autologous and allogeneic HSCT for autoimmune disease from British Society of Blood and Marrow Transplantation registry data. Fifty-five autologous and 15

allogeneic HSCTs were registered. Overall survival (OS) at one and five was 85% and 78%, respectively, in the autologous group and 87% and 65%, respectively, in the allogeneic group. Progression-free survival (PFS) at one and five years was 51% and 33%, respectively, in the autologous group and 80% and 65%, respectively, in the allogeneic group.

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

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

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

In a previous Phase I study involving immune ablative HSCT in 12 patients with refractory Crohn's disease, Burt et al. (2006) reported improvement in symptoms and the Crohn's Disease Activity Index (CDAI) prior to hospital discharge. Improvement in radiographic and colonoscopy findings occurred over months to years following HSCT. Eleven of 12 patients entered a sustained remission defined by a CDAI <150. After a median follow-up of 18.5 months, only one patient developed a recurrence of active CD, which occurred 15 months after HSCT. The authors noted that a randomized study was needed to confirm the effectiveness of this study.

Summary of HSCT for Crohn's Disease: Although preliminary results are promising, larger randomized controlled clinical trials are necessary to determine the safety and effectiveness of hematopoietic stem-cell transplantation (HSCT) for Crohn's disease. At this time the role of HSCT has not been determined for this indication.

Juvenile Idiopathic Arthritis (JIA): Randomized controlled clinical trial data are lacking. Published case reports include outcomes of a single individual. Several small studies, with uncontrolled design have reported a drug-free remission of disease in up to 36% of patients up to five years (Brinkman, 2007; Wulffraat, 2005). In the study by Brinkman et al., at a median follow-up of 80 months, 68% of patients achieved a sustained remission or significant improvement. Treatment-related mortality was 9%. After fatal complications due to macrophage activation syndrome were observed in several patients, the protocol was amended to ensure less profound depletion of T cells, better control of disease prior to transplantation, antiviral prophylaxis, and slower tapering of corticosteroids. The five-year probability of overall survival (OS) was 82%. The probability of disease-free survival (DFS) at five years was 36%. Study limitations include small patient numbers, nonrandomized trial design, and change in treatment protocol during the study.

Summary of HSCT for JIA: 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). The ability to translate these results to the wider population of individuals with MS is limited by heterogeneous patient selection criteria and patient diagnosis, small population size, study design (e.g., lack of randomization for some studies), and short follow-up.

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.

Summary of HSCT for Multiple Sclerosis: 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. Several clinical trials are ongoing for this indication.

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

Systemic Lupus Erythematosus (SLE): Randomized controlled clinical trial data are lacking. Several small, prospective trials and analysis of registry data have reported stability of disease and improvement in quality of life following HSCT (Alchi, 2013; Su, 2013; Song, 2011; Burt, 2006). Alchi reported outcomes of 28 patients who underwent autologous HSCT between 2001 and 2008. Five-year overall survival rate was 81%, disease-free survival was 29%, with a relapse incidence of 56% and non-relapse mortality rate of 15%. In the study by Song et al., the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to evaluate activity. SLEDAI scores significantly ($p<0.01$), although progression-free survival rates were significantly lower in patients receiving conventional therapy compared with those receiving autologous HSCT. There was no significant difference in OS. For this study, the authors note that recruitment of more patients into multi-center, randomized, comparative studies versus conventional treatment of SLE, is warranted to assess the efficacy and safety of autologous HSCT. In the study by Burt et al., (n=50), with a mean follow-up of 29 months, OS was 84%, and probability of disease-free survival (DFS) at five years following HSCT was 50%. Secondary analysis demonstrated stabilization of renal function and improvement in SLEDAI score, anti-nuclear antibody (ANA), antidouble strand deoxyribonucleic acid, complement, and carbon monoxide diffusion capacity. Small patient population and uncontrolled study design limit the ability to apply these study results to the general population of individuals with SLE.

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

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

Vonk et al. (2008) reviewed the outcomes of 26 patients with severe diffuse cutaneous SSc who underwent autologous HSCT. Two patients included in the study were later found to have violated the study inclusion criteria; however, their results were included in the analysis. Two patients (7.1%) died within six months of the procedure. The probability of survival of individuals with at least six month follow-up after HSCT was 96.2% at five years; and 84.8% at seven years. After a median follow-up of 5.2 years, death from disease progression occurred in two patients (8%). Event-free survival rates for patients with at least six months of follow-up after transplantation were 64.3% at five years and 57.1% at seven years. Study limitations included lack of randomization, small participant population, and inclusion of data from ineligible participants.

Additional small phase I and II clinical trials (Oyama, 2007; Nash, 2007) reported improvement in skin scores and stable cardiac, pulmonary, and renal function following nonmyeloablative dose immunosuppressive therapy with autologous HSCT. After median follow-up of 25.5 months, the overall survival (OS) and progression-free survival (PFS) rates were 90% and 70%, respectively, as reported by Oyama, with five-year estimated PFS and OS of 64% in the study by Nash.

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

Use Outside of the US

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

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

Summary

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

Coding/Billing Information

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

Experimental/Investigational/Unproven/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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic 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

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