BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy #: 485
Latest Review Date: January 2022
Category: Surgery

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Proprietary Information of Blue Cross and Blue Shield of Alabama
An Independent Licensee of the Blue Cross and Blue Shield Association

POLICY:

Effective for dates of service on and after March 23, 2019:

Blue Advantage will treat **autologous hematopoietic cell transplantation** as a **covered benefit** as a treatment of systemic sclerosis/scleroderma if all of the following conditions are met:

- adult patients <60 years of age; AND
- maximum duration of condition of 5 years; AND
- modified Rodnan Scale Scores ≥15; AND
- internal organ involvement as noted in the Policy Guidelines; AND
- does not have any exclusion criteria as noted in the Policy Guidelines.

Policy Guidelines:

Autologous HCT should be considered for patients with systemic sclerosis (SSc) only if the condition is rapidly progressing and the prognosis for survival is poor. An important factor influencing the occurrence of treatment-related adverse effects and response to treatment is the level of internal organ involvement. If organ involvement is severe and irreversible, HCT is not recommended. Below are clinical measurements which can be used to guide the determination of organ involvement.

Patients with internal organ involvement indicated by the following measurements may be considered for autologous HCT:

- Cardiac: abnormal electrocardiogram; OR
- Pulmonary: diffusing capacity of carbon monoxide (DLCo) <80% of predicted value; decline of forced vital capacity (FVC) of >10% in last 12 months; pulmonary fibrosis; ground glass appearance on high resolution chest CT; OR
- Renal: scleroderma-related renal disease

Patients with internal organ involvement indicated by the following measurements should not be considered for autologous HCT:

- Cardiac: left ventricular ejection fraction <50%; tricuspid annular plane systolic excursion <1.8 cm; pulmonary artery systolic pressure >40 mm Hg; mean pulmonary artery pressure >25 mm Hg
- Pulmonary: DLCo <40% of predicted value; FVC <45% of predicted value
- Renal: creatinine clearance <40 ml/minute

Blue Advantage will treat **autologous hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma not meeting the above criteria,** as a **non-covered benefit** and as **investigational**.

Blue Advantage will treat **allogeneic hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma** as a **non-covered benefit** and as **investigational**.

Blue Advantage will treat **autologous or allogeneic hematopoietic cell transplantation** as a **non-covered benefit** and as **investigational** as a treatment for autoimmune diseases, including, but not limited to:

- multiple sclerosis
- systemic lupus erythematosus
- juvenile idiopathic or rheumatoid arthritis
- chronic inflammatory demyelinating polyneuropathy
- type 1 diabetes.

Effective for dates of service on or after November 22, 2011 through March 22, 2019:
Blue Advantage will treat **autologous or allogeneic hematopoietic stem-cell transplantation** as a **non-covered benefit** and as **investigational** as a treatment of autoimmune diseases, including, but not limited to:

- systemic sclerosis/scleroderma.
- multiple sclerosis
- systemic lupus erythematosus
- juvenile idiopathic or rheumatoid arthritis
- chronic inflammatory demyelinating polyneuropathy
- type 1 diabetes

Blue Advantage 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 Advantage administers benefits based on the members' contract and 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.

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 (HCT).

Autoimmune Disease Treatment
Immune suppression is a common treatment strategy for many of these diseases, particularly rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, scleroderma). Most patients with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressants, and immunomodulating drugs; however, conventional drug therapies are not curative, and a proportion of patients suffer from autoimmune diseases that range from severe to recalcitrant to rapidly progressive. It is for this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT). The primary concept underlying the use of

HCT for these diseases is this: ablating and "resetting" the immune system can alter the disease process by inducing a sustained remission that possibly leads to cure.

Hematopoietic Cell Transplantation
Hematopoietic stem-cell transplantation (HCT) 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 HCT) or from a donor (allogeneic HCT). 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).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. 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 HLA-A, -B, and –DR 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).

Conditioning for Hematopoietic Cell Transplantation
Conventional Conditioning
The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVH disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation
Reduced-Intensity Conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial GVM effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

KEY POINTS:

The most recent literature review was performed through December 1, 2021.

Summary of Evidence
For individuals with multiple sclerosis who receive HCT, the evidence includes two RCTs, systematic reviews, and several nonrandomized studies. The relevant outcomes are overall survival (OS), health status measures, quality of life (QOL), and treatment-related mortality (TRM) and morbidity. One RCT compared HCT with mitoxantrone, and the trial reported intermediate outcomes (number of new T2 magnetic resonance imaging lesions); the group randomized to HCT developed significantly fewer lesions than the group receiving conventional therapy. The other RCT compared nonmyeloablative HCT results in patients with continued disease-modifying therapy and found a benefit to HCT in prolonged time to disease progression. The findings of the nonrandomized studies revealed improvements in clinical parameters following HCT compared with baseline. Adverse event rates were high, and most studies reported treatment-related deaths. Controlled trials (with appropriate comparator therapies) reporting on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes three RCTs and observational studies. The Relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. All three RCTs compared cyclophosphamide conditioning plus autologous HCT with cyclophosphamide alone. Patients in the RCTs were adults <60 years of age, maximum duration of disease of 5 years, with modified Rodnan skin scores >15, and internal organ involvement. Patients with severe and irreversible organ involvement were excluded from the trials. Short-term results of the RCTs show higher rates of adverse events and TRM among patients receiving autologous HCT compared with patients receiving chemotherapy alone. However, long-term improvements (four years) in clinical outcomes such as modified Rodnan skin scores and forced vital capacity, as well as overall mortality in patients receiving HCT compared with patients receiving cyclophosphamide alone, were consistently reported in all RCTs. Due to sample size limitations in two of the RCTs,

statistical significance was found only in the larger RCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.
For individuals with systemic lupus erythematosus who receive HCT, the evidence includes a systematic review and case series. The relevant outcomes are OS, symptoms, QOL, and TRM and morbidity. Studies were heterogeneous in conditioning regimens and source of cells. The largest series (n=50) reported an overall 5-year survival rate of 84% and the probability of disease-free survival was 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with juvenile idiopathic or rheumatoid arthritis who receive HCT, the evidence includes registry data and a case series. The relevant outcomes are OS, symptoms, QOL, and TRM and morbidity. The registry included 50 patients with juvenile idiopathic or rheumatoid arthritis. The overall drug-free remission rate was approximately 50% in the registry patients and 69% in the smaller case series. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with chronic inflammatory demyelinating polyneuropathy who receive HCT, the evidence includes case reports. The relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with type 1 diabetes who receive HCT, the evidence includes case series and a meta-analysis of 22 studies. The relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. While a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high. A meta-analysis further revealed that HCT is more effective in patients with type 1 diabetes compared with type 2 diabetes and when HCT is administered soon after the diagnosis. Certain factors limit the conclusions that can be drawn about the overall effectiveness of HCT in treating diabetes; those factors are heterogeneity in the stem cell types, cell number infused, and infusion methods. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes 1 RCT and small retrospective studies. The relevant outcomes are OS, symptoms, health status measures, QOL, and TRM and morbidity. The RCT was conducted on patients with Crohn disease. At one-year follow-up, one patient in the control group and two patients in the HCT group achieved remission. Data are needed from additional controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation

In 2020, the American Society for Blood and Marrow Transplantation published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial setting. Table 1 lists guidelines for specific indications addressed in this evidence review.

Table 1. Recommendations for the Use of HCT to Treat Autoimmune Diseases

Indications for HCT in Pediatric Patients (Generally <18 y)	Allogeneic HCT	Autologous HCT
Juvenile rheumatoid arthritis	D	R
Systemic sclerosis	D	R
Other autoimmune and immune dysregulation disorders	R	N
Indications for HCT in Adults >18 y		
Multiple sclerosis	N	C
Systemic sclerosis	N	S
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn disease	N	D
Polymyositis-dermatomyositis	N	D

a "Standard of care (S): This category includes indications that are well defined and are generally supported by evidence in the form of high quality clinical trials and/or observational studies (eg, through CIBMTR or EBMT)." "Standard of care, clinical evidence available (C): This category includes indications for which large clinical trials and observational studies are not available. However, HCT/immune effector cell therapy (IECT) has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multi-center cohort studies. HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits. As more evidence becomes available, some indications may be reclassified as 'Standard of Care'." "Standard of care, rare indication (R): Indications included in this category are rare diseases for which clinical trials and observational studieswith sufficient number of patients are not currently feasible because of their very low incidence. However, single-center or multicenter or registry studies in relatively small cohorts of patients have shownHCT/IECT to be effective treatment with acceptable risks of morbidity and mortality. For

patients withdiseases in this category, HCT/IECT can be considered as a treatment option for individual patients aftercareful evaluation of risks and benefits." “Developmental; (D): Developmental indications include diseases where pre-clinical and/or early phase clinical studies show HCT/IECT to be a promising treatment option. HCT/IECT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as ‘Standard of Care, Clinical Evidence Available’ or ‘Standard of Care’.” “Not generally recommended (N): HCT/IECT is not currently recommended for these indications where evidence and clinical practice do not support the routine use of HCT/IECT. However, this recommendation does not preclude investigation of HCT/IECT as a potential treatment and may be pursued for these indications within the context of a clinical trial.

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 Idiopathic Arthritis, Type I Diabetes Mellitus, JIA

APPROVED BY GOVERNING BODIES:
The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

BENEFIT APPLICATION:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT 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	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; 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	Diagnostic bone marrow; aspiration(s)
38221	Diagnostic bone marrow; biopsy(ies),
38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s) (Effective 01/01/2018)
38230	Bone marrow harvesting for transplantation; allogeneic
38232	; autologous
38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic
38241	;autologous
0489T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands; adipose tissue harvesting, isolation and preparation of harvested cells including incubation with cell dissociation enzymes, removal of non-viable cells and debris, determination of concentration and dilution of regenerative cells (Effective 01/01/2018)
0490T	Autologous adipose-derived regenerative cell therapy for scleroderma in the hands;

	multiple injections in one or both hands (Effective 01/01/2018)

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)

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POLICY HISTORY:

Adopted for Blue Advantage, September 2011
Available for comment October 5 through November 21, 2011
Medical Policy Group, December 2011
Medical Policy Group, October 2012
Medical Policy Group, October 2013
Available for comment October 16 through November 30, 2013
Medical Policy Group, October 2014
Medical Policy Group, March 2015
Medical Policy Group, February 2016
Medical Policy Group, August 2017
Medical Policy Group, December 2017
Medical Policy Group, February 2018
Medical Policy Group, February 2019
Medical Policy Group, March 2020
Medical Policy Group, January 2021
Medical Policy Group, January 2022

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.