Corporate Medical Policy

Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

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Description of Procedure or Service

Most patients with autoimmune disorders respond to conventional therapies. However, these drugs are not curative, and a proportion of patients will have severe, recalcitrant, or rapidly progressive disease. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic stem-cell transplantation (HSCT).

Autoimmune Diseases

Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis/scleroderma, and chronic immune demyelinating polyneuropathy (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, 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 Stem-Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole body radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous 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). Cord blood is discussed in greater detail in policy, Cord Blood as a Source of Stem Cells.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Autologous Stem-Cell Transplantation for Autoimmune Diseases

The goal of autologous HSCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablation) 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 lymphoablative and myeloablative regimens are used. The efficacy of the different conditioning regimens has not been compared in clinical trials.

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

Allogeneic Stem-Cell Transplantation for Autoimmune Diseases

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

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for hematopoietic stem cell transplantation for autoimmune disease when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some health benefit plans may exclude benefits for transplantation.

When Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases is covered

Autologous hematopoietic cell transplantation is considered **medically necessary** as a treatment of systemic sclerosis/scleroderma if **ALL** of the following conditions are met:

- adult patients <69 years of age; **AND**
- maximum duration of scleroderma of 5 years; **AND**
- modified Rodnan Scale Scores ≥15; **AND**
- internal organ involvement as noted in the Policy Guidelines; **AND**
- history of < 6 months treatment with cyclophosphamide; **AND**
- no active gastric antral vascular ectasia; **AND**
- no exclusion criteria as noted in the Policy Guidelines.

When Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases is not covered

Autologous or allogeneic hematopoietic stem-cell transplantation is considered **investigational** as a treatment of autoimmune diseases, including, but not limited to, the following:

- multiple sclerosis (MS)
- juvenile idiopathic or rheumatoid arthritis (RA)
- systemic lupus erythematosus (SLE)
- type 1 diabetes
- chronic inflammatory demyelinating polyneuropathy

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 in the SCOT trial were eligible if they had pulmonary or renal involvement. Pulmonary involvement required active interstitial disease (as determined by bronchoalveolar cell composition or ground-glass opacities on CT of the chest), plus either a forced vital capacity or a diffusing capacity of the lung for carbon monoxide (DLco) of less than 70% of the predicted value. Renal involvement required previous scleroderma-related renal disease.

Patients in the ASTIS trial were eligible if they had diffuse cutaneous systemic sclerosis and involvement of heart, lungs or kidneys.

Exclusion criteria in the SCOT trial were DLco of less than 40% of predicted value, an FVC of less than 45% of the predicted value, left ventricular ejection fraction of less than 50%, a creatinine clearance of less than 40 mL per minute, and pulmonary arterial hypertension.
Exclusion criteria in the ASTIS trial were severe major organ involvement including severe pulmonary arterial hypertension (mean pulmonary artery pressure >50 mm Hg) or serious comorbidities.

For individuals with systemic sclerosis/scleroderma who receive HSCT, the evidence includes 3 RCTs and observational studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. All three RCTs compared cyclophosphamide conditioning plus autologous HCT with cyclophosphamide alone. Patients in the RCTs were adults (up to 69 years of age in one trial), maximum duration of disease of 5 years, with modified Rodnan skin scores $\geq$15, and internal organ involvement. Patients with severe and irreversible organ involvement were excluded from the trials. Short-term results of the RCTs showed higher rates of adverse events and transplant-related mortality 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 multiple sclerosis who receive HSCT, the evidence includes a randomized controlled trial (RCT) and several case series. Relevant outcomes are overall survival, health status measures, quality of life, treatment-related mortality and treatment-related morbidity. The phase 2 RCT compared HSCT to mitoxantrone and reported intermediate outcomes (number of new T2 magnetic resonance imaging lesions); the group randomized to HSCT developed significantly fewer lesions than the group receiving conventional therapy. Findings of case series showed improvements in clinical parameters following HSCT compared to baseline. Adverse event rates were high, and most studies reported treatment-related deaths. Controlled trials with appropriate comparator therapies that report on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have juvenile idiopathic or rheumatoid arthritis who receive HSCT, the evidence includes registry data and a case series. Relevant outcomes are symptoms, quality of life, medication use, treatment-related mortality, and treatment-related morbidity. The registry study included 50 patients and 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 systemic lupus erythematosus who receive HSCT, the evidence includes a systemic review and case series. Relevant outcomes are overall survival, symptoms, quality of life, treatment-related mortality, and treatment-related morbidity. Studies were heterogeneous in conditioning regimens and source of cells. The largest series (N=50 patients) found 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 type 1 diabetes who receive HSCT, the evidence includes case series and a meta-analysis of 22 studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. While a substantial proportion of patients tended to become insulin free after HSCT, remission rates were high. The 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 chronic inflammatory demyelinating polyneuropathy who receive HSCT, the evidence includes case reports. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related 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 other autoimmune diseases (eg, Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes 1 RCT and small retrospective studies. Relevant outcomes include overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. The RCT was conducted on patients with Crohn disease. At 1 year followup, 1 patient in the control group and 2 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: *38205, 38206, 38208, 38209, 38230, 38232, 38240, 38241, 38242, 38243, S2150*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

Bone Marrow Transplant for Autoimmune Disease

BCBSA Medical Policy Reference Manual, 12/1/1999

BCBSA TEC Evaluation, Tab 1, June 2000

BCBSA Medical Policy Reference Manual, 8/18/2000

ECRI Health Technology Assessment; Executive Briefings, Sept. 2000; No. 93

BCBSA TEC Evaluation 2001

BCBSA Medical Policy Reference Manual, 2/15/2002; 8.01.25

Specialty Matched Consultant Advisory Panel - 11/2002

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 7/15/2004

Specialty Matched Consultant Advisory Panel - 11/2004

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 4/25/06

Specialty Matched Consultant Advisory Panel - 11/2006

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 9/11/08

Specialty Matched Consultant Advisory Panel - 11/2008

Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 9/10/2009

Specialty Matched Consultant Advisory Panel - 11/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 9/16/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 9/1/2011

Specialty Matched Consultant Advisory Panel – 11/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 9/12/2012

Specialty Matched Consultant Advisory Panel 12/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 10/10/2013

Specialty Matched Consultant Advisory Panel 11/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 10/9/2014

Specialty Matched Consultant Advisory Panel 11/2014

Specialty Matched Consultant Advisory Panel 11/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 1/14/2016

Specialty Matched Consultant Advisory Panel 11/2016

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 7/13/2017

Specialty Matched Consultant Advisory Panel 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 1/11/2018

Specialty Matched Consultant Advisory Panel 11/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.25, 1/17/2019

Medical Director review 2/2019

Specialty Matched Consultant Advisory Panel 11/2019

Medical Director review 11/2019

Policy Implementation/Update Information

Bone Marrow Transplant for Autoimmune Disease

1/01 Specialty Matched Consultant Advisory Group.

2/01 Original policy issued.

5/02 Policy statement reaffirmed and reference sources added. Codes 38220 and 38221 added to Billing and Coding section.

2/03 Specialty Matched Consultant Advisory Panel review 11/2002. No change in criteria. Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.

1/04 Benefits Application and Billing/Coding sections updated for consistency.

2/04 Individual CPT codes listed for CPT code ranges 38240-38242 under Billing/Coding section.

7/29/04 HCPCS code S2150 added to Billing/Coding section.

12/9/04 Specialty Matched Consultant Advisory Panel review 11/29/2004. No change to criteria. Description of Procedure or Service revised. Rationale added in Policy Guidelines section. Policy number added to Policy Key Words section. Hematopoietic and Opportunistic added to Definitions. References added.

12/11/06 Specialty Matched Consultant Advisory Panel review 11/6/06. No changes to policy statement. Added the following statement to the "Policy" section; Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services for Life-Threatening Conditions. Updated rationale in "Policy Guidelines" section. References added.

12/22/08 Specialty Matched Consultant Advisory Panel review 11/13/2008. No change to policy statement. "Policy Guidelines" section updated. References added. (btw)

6/22/10 Policy Number(s) removed. (amw)

Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

1/4/11 Policy name changed from “Bone Marrow Transplant for Autoimmune Diseases” to “Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases”. Specialty Matched Consultant Advisory Panel review 11/29/10. No change to policy statement. (btw)

3/1/11 “Description” section revised. Added indications of juvenile idiopathic arthritis and diabetes mellitus to the “When Not Covered” section as investigational. No change to intent of policy. “Policy Guidelines” updated. References added. Medical Director review 2/9/2011. (btw)

1/10/12 Specialty Matched Consultant Advisory Panel review 11/30/11. No change to policy statement. References added. (btw)

2/21/12 New 2012 CPT code 38232 added to Billing/Coding section. (btw)

12/28/12 Specialty Matched Consultant Advisory Panel review 12/4/2012. No change to policy statement. Reference added. Added new 2013 CPT code, 38243 to Billing/Coding section. (btw)

12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/2013. Added "chronic inflammatory demyelinating polyneuropathy" as an investigational indication. Reference added. (btw)

12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. Reference added (lpr)

12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. No change to policy statement. (lpr)

4/1/16 Updated Policy Guidelines section. No change to policy intent. Reference added. (lpr)

12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)

8/11/17 Updated Policy Guidelines section. Reference added. No change to policy intent. (lpr)

12/15/17 Specialty Matched Consultant Advisory Panel review 11/29/2017. No change to policy statement. (lpr)

1/15/19 Specialty Matched Consultant Advisory Panel review 11/2018. Reference added. No change to policy statement. (lpr)

2/26/19 Added medically necessary criteria for systemic sclerosis. Policy statement changed from investigational to medically necessary. Added guidelines for internal organ involvement to Policy Guidelines section. Medical Director review 2/2019. Reference added. (lpr)

12/31/19 Specialty Matched Consultant Advisory Panel review 11/20/2019. No change to policy statement. (lpr)