Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

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.

HSCT in autoimmune disorders raises the question of whether ablating and “resetting” the immune system can alter the disease process and sustain remission and possibly lead to cure.

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem cell transplantation (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 “naive” 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
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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**

Hematopoietic stem-cell transplantation for Autoimmune Diseases is considered investigational
for all applications. BCBSNC does not cover investigational services or procedures.

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**

Not applicable.
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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)
- systemic sclerosis/scleroderma
- type 1 diabetes
- chronic inflammatory demyelinating polyneuropathy

Policy Guidelines

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. 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%. 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 case series (total N=91 patients). Relevant outcomes are overall survival, symptoms, quality of life, treatment-related mortality, and treatment-related morbidity. Several case series have been published. 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 systemic sclerosis/scleroderma who receive HSCT, the evidence includes RCTs and observational studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, treatment-related mortality, and treatment-related morbidity. The results of the ASTIS trial suggest high-dose chemotherapy with autologous HSCT may improve survival among patients with diffuse cutaneous systemic sclerosis compared with pulsed intravenous cyclophosphamide. However, analysis of the internal validity of the trial using U.S. Preventive Services Task Force criteria showed fatal flaws and a poor study rating due to attrition in the control group that could have skewed the survival curve to show better survival for HSCT recipients than for controls. A smaller RCT (N=19) found that the rate of improvement at 12 months was significantly higher in the HSCT group than in the conventional therapy group. Data from these studies are inconclusive; additional studies are needed to confirm safety and efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.
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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 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 with 1 to 3 patients each. 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 small retrospective studies. Relevant outcomes include overall survival, symptoms, health status measures, quality of life, and treatment-related mortality 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.

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, 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 TEC Evaluation, Tab 1, June 2000


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

BCBSA TEC Evaluation 2001


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Specialty Matched Consultant Advisory Panel 12/2012
Specialty Matched Consultant Advisory Panel 11/2017

Policy Implementation/Update Information

**Bone Marrow Transplant for Autoimmune Disease**

2/01 Original policy issued.
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5/02  Policy statement reaffirmed and reference sources added. Codes 38220 and 38221 added to Billing and Coding section.


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.


12/11/06  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.


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)


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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)

Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.