Medical Policy
Hematopoietic Cell Transplantation for Autoimmune Diseases

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Policy Number: 192
BCBSA Reference Number: 8.01.25
NCD/LCD: NA

Related Policies
Plasma Exchange #466

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

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

- Multiple sclerosis
- Systemic lupus erythematosus
- Juvenile idiopathic or rheumatoid arthritis
- Chronic inflammatory demyelinating polyneuropathy
- Type 1 diabetes mellitus.

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 <60 years of age; AND
- Maximum duration of condition of 5 years; AND
- Modified Rodnan Scale Scores ≥15; AND
- Internal organ involvement*; AND
- History of < 6 months treatment with cyclophosphamide; AND
- No active gastric antral vascular ectasia; AND
- Do not have any exclusion criteria. **

*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 or 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.

Autologous hematopoietic cell transplantation as a treatment of systemic sclerosis/scleroderma not meeting the above criteria is considered INVESTIGATIONAL.

Prior Authorization Information
Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
- For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
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</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is required.</td>
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<tr>
<td>Medicare HMO BlueSM</td>
<td>Prior authorization is required.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>Prior authorization is required.</td>
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</tbody>
</table>

Description
Autoimmune Diseases
Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including multiple sclerosis, systemic sclerosis/scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and chronic immune demyelinating polyneuropathy. The National Institutes of Health has estimated that 5% to 8% of Americans have an autoimmune disorder.

The pathogenesis of autoimmune diseases is not well understood, but it 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).

Treatment
Immune suppression is a common treatment strategy for many of these diseases, particularly the rheumatic diseases (eg, 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.¹

**Hematopoietic Cell Transplantation**

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or 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 considered antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in policy #285.

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 critical for achieving a good outcome with allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of 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 HCT**

The goal of autologous HCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablation) and generate new, self-tolerant lymphocytes.² This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablation), as is often performed in autologous HCT for hematologic malignancies.² Both lymphoablative and myeloablative regimens are used in patients with an autoimmune disease; however, there is no standard conditioning regimen.¹ The efficacy of the different conditioning regimens has not been compared in clinical trials.¹

Currently, for autoimmune diseases, autologous transplant is preferred over allogeneic, in part because of the lower toxicity of autotransplant relative to allogeneic, the graft-versus-host disease associated with the allogeneic transplant, and the need to administer posttransplant immunosuppression after an allogeneic transplant.¹

**Allogeneic HCT**

Experience of using allogeneic HCT for autoimmune diseases is currently limited,¹ 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.¹

**Summary**

Most patients with autoimmune disorders respond to conventional drug therapies; however, conventional drug therapies are not curative—and a proportion of patients suffer from autoimmune diseases that range from the severe to the recalcitrant to the rapidly progressive. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT).

For individuals with multiple sclerosis who receive HCT, the evidence includes a randomized controlled trial (RCT) and several case series. The relevant outcomes are overall survival (OS), health status measures, quality of life (QOL), and treatment-related mortality (TRM) and morbidity. The phase 2 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 findings of the case series 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 (eg, Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes one 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.

Policy History
### Date | Action
---|---
1/2019 | Outpatient prior authorization is required for all commercial products including Medicare Advantage. Effective 1/1/2019.
2/2018 | New references added from BCBSA National medical policy.
10/2016 | Clarified coding information.
12/2014 | New references added from BCBSA National medical policy.
6/2014 | Updated Coding section with ICD10 procedure and diagnosis codes. Effective 10/2015.
12/2012 | Updated to add new CPT code 38243.

**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:

- [Medical Policy Terms of Use](#)
- [Managed Care Guidelines](#)
- [Indemnity/PPO Guidelines](#)
- [Clinical Exception Process](#)
- [Medical Technology Assessment Guidelines](#)

**References**

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; autologous</td>
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</tbody>
</table>

### HCPCS Codes

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<tr>
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</table>

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)

### ICD-10 Procedure Codes

<table>
<thead>
<tr>
<th>ICD-10-PCS procedure codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>30233G0</td>
<td>Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233G1</td>
<td>Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233X0</td>
<td>Transfusion of Autologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233X1</td>
<td>Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233Y0</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233Y1</td>
<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243G0</td>
<td>Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243G1</td>
<td>Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach</td>
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<td>30243Y0</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach</td>
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<tr>
<td>30243Y1</td>
<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30263G0</td>
<td>Transfusion of Autologous Bone Marrow into Central Artery, Percutaneous Approach</td>
</tr>
<tr>
<td>30263G1</td>
<td>Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach</td>
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<td>3E03305</td>
<td>Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach</td>
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<td>3E05305</td>
<td>Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach</td>
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