

# Protocol

## Hematopoietic Cell Transplantation for Autoimmune Diseases

(80125)

<b>Medical Benefit</b>		<b>Effective Date:</b> 06/01/19	<b>Next Review Date:</b> 11/20
<b>Preauthorization</b>	Yes	<b>Review Dates:</b> 04/07, 05/08, 01/10, 01/11, 01/12, 01/13, 01/14, 11/14, 11/15, 11/16, 11/17, 11/18, 03/19, 11/19	

***Preauthorization is required and must be obtained through Case Management.***

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With multiple sclerosis</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Hematopoietic cell transplantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional medication therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With systemic sclerosis/scleroderma</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Hematopoietic cell transplantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional medication therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Symptoms</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With systemic lupus erythematosus</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Hematopoietic cell transplantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional medication therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Symptoms</li> <li>• Quality of life</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With juvenile idiopathic or rheumatoid arthritis</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Hematopoietic cell transplantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional medication therapy</li> <li>• Biologic therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Symptoms</li> <li>• Quality of life</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With chronic inflammatory demyelinating polyneuropathy</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Hematopoietic cell transplantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional medication therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Symptoms</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With type 1 diabetes</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Hematopoietic cell transplantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional medication therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Symptoms</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis)</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Hematopoietic cell transplantation</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Conventional medication therapy</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Symptoms</li> <li>• Health status measures</li> <li>• Quality of life</li> <li>• Treatment-related mortality</li> <li>• Treatment-related morbidity</li> </ul>

## DESCRIPTION

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).

## SUMMARY OF EVIDENCE

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 two 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 five 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 hetero-

geneous in conditioning regimens and source of cells. The largest series (n=50) reported an overall five 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. 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 one RCT and small retrospective studies. 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

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.

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 under 60 years of age; AND
- maximum duration of condition of five years; AND

- modified Rodnan Scale Scores 15 or greater; AND
- internal organ involvement as noted in the Policy Guidelines; AND
- history of less than six months treatment with cyclophosphamide; AND
- no active gastric antral vascular ectasia; AND
- do not have any exclusion criteria as noted in the Policy Guidelines.

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

### **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) less than 80% of predicted value; decline of forced vital capacity (FVC) of 10% or greater 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 less than 50%; tricuspid annular plane systolic excursion less than 1.8 cm; pulmonary artery systolic pressure greater than 40 mm Hg; mean pulmonary artery pressure greater than 25 mm Hg
- Pulmonary: DLCo less than 40% of predicted value; FVC less than 45% of predicted value
- Renal: creatinine clearance less than 40 ml/minute

### **MEDICARE ADVANTAGE**

If a transplant is needed, we arrange to have the Medicare-approved transplant center review and decide whether the patient is an appropriate candidate for the transplant.

### **BACKGROUND**

#### **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 (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.<sup>1</sup>

#### 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 detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

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.<sup>2</sup> This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablation), as is often performed in autologous HCT for hematologic malignancies.<sup>2</sup> Both lymphoablative and myeloablative regimens are used in patients with an autoimmune disease; however, there is no standard conditioning regimen.<sup>1</sup> The efficacy of the different conditioning regimens has not been compared in clinical trials.<sup>1</sup>

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.<sup>1</sup>

#### ALLOGENEIC HCT

Experience of using allogeneic HCT for autoimmune diseases is currently limited,<sup>1</sup> 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.<sup>1</sup>

## REGULATORY STATUS

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.

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Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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