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.

Description

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).

Summary of Evidence

Initial studies focused on using hematopoietic stem-cell transplantation (HSCT) as salvage therapy for treatment of refractory autoimmune diseases. More recent experience has better helped to define which patients are most likely to benefit from HSCT, and the field has shifted to the use of HSCT earlier in the disease course before irreversible organ damage and to the use of safer and less intense nonmyeloablative conditioning regimens.

The experience with HSCT and autoimmune disorders has been predominantly with autologous transplants, and a number of published clinical reports with follow-up have demonstrated the safety and in some patients (particularly those with systemic sclerosis, systemic lupus erythematosus, and multiple sclerosis [MS]) the impact of HSCT in selected autoimmune diseases.

The results of the Autologous Stem Cell Transplantation International Scleroderma (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 compared with controls. The investigators acknowledge this limitation in addition to stating that the unblinded outcome assessments may have influenced results, and wide confidence intervals for some secondary outcomes indicated less certainty about those results. An accompanying editorial concurs that autologous HSCT to treat systemic sclerosis requires further study before it should be offered to patients in routine clinical practice.31

Although some of the initial results have been promising, this field continues to evolve. Many trials (randomized and nonrandomized) are currently recruiting or ongoing comparing the use of HSCT with conventional therapy for most of the diseases addressed in this Protocol; the results of these trials will further define the role of HSCT.
in the management of these diseases. Thus, use of HSCT for these autoimmune diseases is considered investigational.

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

• multiple sclerosis
• juvenile idiopathic and rheumatoid arthritis
• systemic lupus erythematosus
• systemic sclerosis/scleroderma
• type 1 diabetes mellitus
• chronic inflammatory demyelinating polyneuropathy.

Medicare Advantage
If a transplant is needed, we arrange to have the 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 MS, rheumatoid arthritis (RA), SLE, systemic sclerosis/scleroderma, and chronic immune demyelinating polyneuropathy. The National Institutes of Health estimates that 5% to 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, scleroderma). Most patients with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressants, and immunomodulating drugs. 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 HSCT. The primary concept underlying use of HSCT for these diseases is that ablating and “resetting” the immune system can alter the disease process, first inducing a sustained remission that possibly leads to cure.

HSCT
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 HSCT) or from a donor (allogeneic HSCT). 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 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 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.\(^2\) This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablation), as is often performed in autologous HSCT for hematologic malignancies.\(^2\) However, no standard conditioning regimen exists for autoimmune diseases and both lymphoablative and myeloablative regimens are used.\(^1\) 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 GVHD associated with allogeneic transplant, and the need to administer posttransplant immunosuppression after an allogeneic transplant.\(^1\)

**Allogeneic Stem-Cell Transplantation for Autoimmune Diseases**

The experience of using allogeneic HSCT 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.\(^1\)

**Regulatory Status**

Hematopoietic stem-cell transplantation is not a U.S. Food and Drug Administration–regulated procedure.


