Clinical Policy Title: Stem cell transplants for autoimmune disease

Clinical Policy Number: 18.03.02

**Effective Date:** April 1, 2016
**Initial Review Date:** June 16, 2013
**Most Recent Review Date:** January 11, 2018
**Next Review Date:** January 2019

Related policies:

- CP# 14.02.06  Bone marrow transplants
- CP# 05.03.02  Stem cell transplants for breast cancer

ABOUT THIS POLICY: Select Health of South Carolina has developed clinical policies to assist with making coverage determinations. Select Health of South Carolina’s clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by Select Health of South Carolina when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Select Health of South Carolina’s clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Select Health of South Carolina’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Select Health of South Carolina will update its clinical policies as necessary. Select Health of South Carolina’s clinical policies are not guarantees of payment.

**Coverage policy**

Select Health of South Carolina considers the use of autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplant (single or planned tandem) to be investigational, and not medically necessary as a treatment for autoimmune diseases and autoimmune-related diseases including, but not limited to:

- Celiac sprue disease.
- Crohn’s disease.
- Graves’ disease.
- Juvenile idiopathic arthritis.
- Multiple sclerosis.
- Neuromyelitis optica.
- Pernicious anemia.
- Rheumatoid arthritis.
- Sjögren’s syndrome.
- Systemic lupus erythematosus.
- Systemic sclerosis (scleroderma).
- Systemic vasculitis.
- Type 1 diabetes
- Ulcerative colitis.

Note: A complete list of autoimmune diseases is available at the American Autoimmune Related Diseases Association’s website, www.aarda.org/autoimmune-information/list-of-diseases/.

Limitations:

All other uses of autologous or allogeneic (ablative and non-myeloablative [mini-transplant]) hematopoietic stem cell transplant, single or planned tandem, are not medically necessary.

Alternative covered services:

Plan approved treatment ordered by treating participating provider.

Background

Stem cells that form blood and immune cells are ultimately responsible for the constant renewal of blood. A bone marrow transplant, also called a hematopoietic stem cell transplant, is a procedure that replaces damaged or destroyed bone marrow with healthy bone marrow stem cells. Bone marrow is the soft, fatty tissue inside the bones. There are three basic kinds of stem cell transplants:

Autologous bone marrow transplant:
- The term auto means self. Stem cells are removed from a patient prior to receiving high-dose chemotherapy or radiation treatment. The stem cells are stored in a freezer (cryopreservation). After high-dose chemotherapy or radiation treatments, stem cells are put back in the body to regenerate normal blood cells. This is called a rescue transplant.

Allogeneic bone marrow transplant:
- The term allo means other. Stem cells are removed from another person, called a donor. Most times, the donor’s genes must at least partly match the member’s genes. Special blood tests are done to see if a donor is a good match for the member. A brother or sister is most likely to be a good match. Sometimes parents, children, and other relatives are good matches. Donors who are not related to members may be found through national bone marrow registries.

Syngeneic stem cell transplants:
- This is a special kind of allogenic transplant that can only be used when the recipient has an
identical sibling (twin or triplet) who can donate — someone who has the same tissue type. An advantage of syngeneic stem cell transplant is that graft-versus-host disease will not be a problem. No cancer cells should be present in a transplant, as there should be no cancer cells in an autologous transplant (American Cancer Society [ACS], 2016).

Some people may have a hematopoietic stem cell transplant using stem cells from umbilical cord blood. There are cord blood banks that store blood taken from umbilical cords. After the baby is born and the umbilical cord has been cut, a doctor extracts blood from the umbilical cord, and placenta. The blood bank may give the donated stem cells to a person whose blood cells closely match the donated cells. These transplants are mostly used for children, because of the lower volume of cells collected. It may be possible for adults to have a hematopoietic stem cell transplant from two different umbilical cords (double cord transplant).

The term autoimmune disease refers to a varied group of illnesses that involve almost every human organ system. It includes diseases of the nervous, gastrointestinal, and endocrine systems, as well as skin and other connective tissues, eyes, blood, and blood vessels. In all of these autoimmune diseases, the underlying problem is autoimmunity — the body’s immune system becomes misdirected and attacks the very organs it was designed to protect.

Autoimmune diseases are a group of highly heterogeneous disorders with variable organ system involvement, diverse etiologies and pathologies, and different prognoses (Burt, 2008). Standard treatment for autoimmune diseases generally consists of immunosuppression, anti-inflammatory and/or anti-malarial medication, and supportive care. Dose escalation of immunosuppressive medication using hematopoietic stem cell transplant is being proposed for individuals who are refractory to standard treatment, or have disease considered to be life or organ threatening. Autoimmune disease, of which there are as many as 80 types, affects up to 50 million Americans, according to the American Autoimmune Related Diseases Association (AARDA, 2017).

The most common autoimmune diseases include Addison’s disease, celiac sprue disease, Graves disease, Hashimoto’s disease, inflammatory bowel disease, pernicious anemia, psoriasis, rheumatoid arthritis, reactive arthritis, scleroderma, Sjögren’s syndrome, systemic lupus erythematosus, type 1 diabetes, and vitiligo.

Most hematopoietic stem cell transplant procedures for autoimmune disease treated multiple sclerosis, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, juvenile idiopathic arthritis, and immune cytopenias (Passweg, 2007). The current number of autoimmune disease patients treated with hematopoietic stem cell transplants worldwide now exceeds 2,000 (Rebeiro, 2016).

**Searches**

Select Health of South Carolina searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.

The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on December 5, 2017. Search terms were: “autoimmune diseases,” “stem cell transplant” (MeSH), and “multiple sclerosis.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.

- **Guidelines based on systematic reviews.**

- **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Very few professional guidelines address hematopoietic stem cell transplants for autoimmune disease. The latest European Group for Blood and Marrow Transplant guideline emphasizes the need for more studies, and systematic data reporting within studies before evidence-based recommendations can be made (Snowden, 2012). The National Institute for Health and Clinical Excellence (NICE) issued a guideline on Crohn’s disease (an autoimmune disease), but it did not address stem cell transplants as a treatment option (NICE, 2012). The 2017 update of the European League against rheumatism recommendations for treating systemic sclerosis did not include any new recommendations for hematopoietic stem cell transplants (Kowal-Bielecka, 2017).

While hematopoietic stem cell transplants for various autoimmune diseases have been the subject of various articles, these are limited for judging medical necessity. One article notes that studies of transplants for multiple sclerosis show some improvement, but conclusions are limited because they lack control groups, lack information on disease course before treatment, and have almost no long-term follow-up (Bahuraysah, 2016).

The disorder most studied in efficacy of stem cell transplants is multiple sclerosis. A review of eight case series rated outcomes for multiple sclerosis patients with transplants versus those refractory to conventional treatment; higher progression free survival up to three years was observed (Reston, 2011). A meta-analysis of multiple sclerosis patients including six or eight single-arm clinical trial studies documented a 38 percent improvement in expanded disability status scale score 12 months after transplant compared to baseline, but cautioned that these results represented small evidence bases (Li, 2016). A third meta-analysis on immunoablative therapy followed by autologous hematopoietic stem cell transplantation to manage severe and treatment-refractory multiple sclerosis included 15 studies.
The overall transplant-related mortality of 2.1 percent, has declined over time, and the percentages of disease-free patients after two and five years were 83 and 67 (Sormani, 2017).

A recent review of 38 studies (n=344) of skin sclerosis and lung function in systemic sclerosis showed improvement in skin thickening, maintained for eight years. Forced vital capacity slightly (but significantly) improved after one to two years. Authors concluded that the safety of these transplants was acceptable (Eryaud, 2017). Another review of nine articles (only two randomly controlled) concluded that progression-free survival and quality-of-life measures were superior in transplant patients, compared to those given monthly cyclophosphamide (Host, 2017). A Hayes report on autologous stem cell transplantation for systemic sclerosis used 16 studies (n=1,356, one of which was 900) resulted in conflicting findings, making conclusions about safety and effectiveness not possible until a full assessment could be completed (Hayes, 2015).

A systematic review of 25 studies (n=279) of patients with systemic lupus erythematosus who received a transplant mostly reported improvement in disease activity control or overall survival; authors describe these results as “promising” but also “preliminary” (Leone, 2017).

There are only a few other meta-analyses and systematic reviews on hematopoietic stem cell transplants for autoimmune disease. Both are based on small numbers of subjects. One reviewed 11 studies (n=169) for Crohn’s disease patients, which showed some remission in 50 percent to 100 percent of patients, but also observed relapse in a substantial portion (Hayes, 2017). One analyzed 20 cases of inflammatory bowel disease, finding remission in 17 (Al-toma, 2014). A review of 35 polycythemia vera patients found no evidence basis for treating the disease with hematopoietic stem cell transplants (Cario, 2009).

One large study (n=900) was an analysis of survival after hematopoietic stem cell transplants for a variety of conditions, including multiple sclerosis (n=345), systemic sclerosis (n=175), systemic lupus erythematosus (n=85), rheumatoid arthritis (n=89), juvenile arthritis (n=65), hematologic immune cytopenia (n=37), and all others (102). The five-year survival rate after transplant was 85 percent, and the five-year progression-free survival rate was 43 percent (Farge, 2010).

A major issue for physicians treating autoimmune disease is that although temporary remissions do occur, the conditions are painful and chronic for patients. A growing number of studies suggest that uncontrolled systemic inflammation leads to premature atherosclerosis and cardiovascular deaths, as well as toxicity from chronic immunosuppression, especially glucocorticoids. Despite this, it is still a challenge for a rheumatologist, neurologist, or gastroenterologist to accept an immediate treatment-related mortality of 5 percent to 10 percent, especially because long-term benefits have yet to be demonstrated. The hypothesis is that in a randomized prospective trial of hematopoietic stem cell transplant versus conventional treatment, early toxicity from treatment-related mortality would eventually be surpassed by later deaths and/or organ failure from disease progression in the control arm, but this has yet to be proven.

The peer-reviewed, published scientific research consists of retrospective analyses, small case studies,
feasibility studies, and phase I/II trials that limit the ability to generalize findings to the autoimmune disease population. However, a number of phase III clinical trials are ongoing. Nonstandard patient selection criteria, small patient populations, variability of conditioning regimens used for transplantation, and lack of randomization are reported limitations of many published studies. Although results of published studies are promising, in the absence of outcomes from well-designed randomized controlled trials published in peer-reviewed scientific literature, the role of hematopoietic stem cell transplant for any autoimmune disease has not yet been established.

An early report covering 1,000 patients (including 200 in the U.S.) reported a declining mortality rate over time (Passweb, 2007).

Multiple sclerosis has been described as the lead indication for hematopoietic stem cell transplant treatment (Atkins, 2010), and is the most commonly studied autoimmune disease receiving hematopoietic stem cell transplants in the medical literature. There are no controlled studies comparing hematopoietic stem cell transplant with other therapies for multiple sclerosis or other autoimmune diseases (Pasquini, 2010).

Numerous articles in the medical literature have addressed efficacy of hematopoietic stem cell transplant for treating multiple sclerosis, including:

- Improvements in relapse-free, progression-free, or multiple sclerosis activity-free survival (Burt, 2015; Atkins, 2016; Saccardi, 2006; Fassas, 2010).
- Improvements in Expanded Disability Status Scale scores (Burt, 2015; Shevchenko, 2008; Bowen, 2012).
- Reduction in number and volume of T2 lesions (Burt, 2015; Mancardi, 2015; Shevchenko, 2008).
- Better responses when treatment commences early in the disease (Atkins, 2010).
- Reversal of neurological deficits (Burt, 2009).

Despite these results, a consensus for using hematopoietic stem cell transplants for multiple sclerosis is still lacking among experts, as the number of studies and subjects is insufficient.

**Policy updates:**

An additional three guidelines/other and six peer-reviewed references were added, and 10 peer-reviewed references were removed from this policy in December 2017.

In January 2017, an additional 20 references were added. Most were recent publications or studies specifically on hematopoietic stem cell transplant and multiple sclerosis.

**Summary of clinical evidence:**
### Citation | Content, Methods, Recommendations
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Leone (2017) | **Key points:**
- Systematic review of 25 studies (n=279) of patients with systemic lupus erythematosus who received a hematopoietic stem cell transplant.
- Studies mostly reported improvement in disease activity control or overall survival.
- Authors describe these results as “promising,” but also “preliminary.”

Sormani (2017) | **Key points:**
- Meta-analysis on immunoablative therapy followed by autologous transplantation.
- 15 studies (n=764) of severe and treatment-refractory multiple sclerosis.
- The overall transplant-related mortality of 2.1 percent has declined over time, and the percentages of disease-free patients after two and five years were 83 and 67.

Bahuraysak (2016) | **Key points:**
- Review of studies of transplants for multiple sclerosis.
- Some improvement has occurred, but conclusions are limited because they lack control groups, lack information on disease course before treatment, and have almost no long-term follow-up.

Fange (2010) | **Key points:**
- Study (n=900) analyzing survival after transplants for variety of autoimmune conditions.
- Disorders include multiple sclerosis (n=345), systemic sclerosis (n=175), systemic lupus erythematosus (n=85), rheumatoid arthritis (n=89), juvenile arthritis (n=65), hematologic immune cytopenia (n=37), and all others (102).
- Five-year survival rate (overall and progression free) after transplant were 85 percent and 43 percent.

### References

**Professional society guidelines/other:**


ECRI Institute. Immunoablative therapy with bone marrow or peripheral stem cell transplantation for


**Peer-reviewed references:**


**CMS National Coverage Determinations (NCDs):**

No NCDs identified as of the writing of this policy.

**Local Coverage Determinations (LCDs):**

No LCDs identified as of the writing of this policy.

**Commonly submitted codes**

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

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