



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

**Policy #** 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers autologous or allogeneic hematopoietic cell transplantation (HCT) as a treatment of autoimmune diseases, including, but not limited to the following to be **investigational**.\*

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

### **Background/Overview**

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 HCT.

### **Autoimmune Diseases**

Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including MS, RA, SLE, systemic sclerosis/scleroderma, and 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).

### **Treatment**

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. 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 HCT. The primary concept underlying use of

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

HCT 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.

### **Hematopoietic Cell Transplantation**

Hematopoietic cell transplantation 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 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 cells in it are antigenically “naïve” and thus, are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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 a critical factor for achieving a good outcome of allogeneic HCT. 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 Cell Transplantation**

The goal of autologous HCT 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 HCT 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 Cell Transplantation**

The experience of using allogeneic HCT 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.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

The U.S. FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

### Centers for Medicare and Medicaid Services (CMS)

There are numerous autoimmune diseases and the CMS has not issued a national coverage determination (NCD) for stem cell transplantation for each disease. A general NCD for stem cell transplantation (110.8.1) states the following:

#### a. Nationally Covered Indications

The following uses of allogeneic HSCT [hematopoietic stem-cell transplantation] are covered under Medicare:

- i. Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
- ii. Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
- iii. Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

#### b. Nationally Non-Covered Indications

Effective for services performed on or after May 24, 1996, allogeneic HSCT is not covered as treatment for multiple myeloma.

## 2. Autologous Stem-Cell Transplantation (AuSCT)

#### a. Nationally Covered Indications

- i. Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §1862(a)(1)(A) of the Social Security Act (the Act) for the following conditions and is covered under Medicare for patients with:
  - Acute leukemia in remission who have a high probability of relapse and who have no HLA-matched;
  - Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
  - Recurrent or refractory neuroblastoma; or
  - Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.
- ii. Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and,
- Adequate cardiac, renal, pulmonary, and hepatic function.
  - iii. Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high-dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:
    - Amyloid deposition in 2 or fewer organs; and,
    - Cardiac left ventricular ejection fraction (EF) greater than 45%.
  - b. Nationally Non-Covered Indications  
Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:
    - Acute leukemia not in remission;
    - Chronic granulocytic leukemia;
    - Solid tumors (other than neuroblastoma);
    - Up to October 1, 2000, multiple myeloma;
    - Tandem transplantation (multiple rounds of AuSCT) for patients with multiple myeloma;
    - Effective October 1, 2000, non-primary AL amyloidosis; and,
    - Effective October 1, 2000, thru March 14, 2005, primary AL amyloidosis for Medicare beneficiaries age 64 or older.

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §1862(a)(1)(A) of the Act and is not covered under Medicare.

### **Rationale/Source**

Recent reviews summarize the experience to date with HCT and autoimmune diseases.

As of March 2009, patients with an autoimmune disease registered in the European Group for Blood and Marrow Transplantation/European League Against Rheumatism (EBMT/EULAR) database who have undergone HCT include a total of 1,031 with the clinical indications of MS (n=379), systemic sclerosis (n=207), SLE (n=92), RA (n=88), juvenile idiopathic arthritis (n=70), idiopathic thrombocytopenic purpura (n=23), and Crohn's disease (n=23).

### **Multiple Sclerosis**

Only 1 randomized controlled trial (RCT) evaluating HCT for treatment of MS has been published, but this trial did not report clinical outcomes. No controlled trials with contemporaneous control groups were identified that reported clinical end points such as overall survival (OS), progression-free survival (PFS), or

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

disability status as their primary outcomes. The 2015 RCT by Mancardi et al was originally designed as a phase 3 study reporting on disability progression. However, due to low patient enrollment, the protocol was amended as a phase 2 study with the primary outcome of cumulative number of new T2 magnetic resonance imaging (MRI) lesions in the 4 years after treatment. Eligibility for the trial was secondary progressive or relapsing-remitting MS, a documented worsening during the last year, and lack of response to conventional therapy. A total of 21 patients were randomized to autologous HCT (n=9) or medical therapy (mitoxantrone) (n=12). Follow-up data were not available on 4 patients; missing data was imputed in the intention-to-treat analysis of the primary outcome. The median number of new T2 MRI lesions was 2.5 in the HCT group and 8 in the conventional therapy group (rate ratio, 0.21; 95% confidence interval, 0.10 to 0.48,  $p < 0.001$ ). Among secondary outcomes, the annualized relapse rate was significantly lower in the HCT group (0.19) than in the conventional therapy group (0.6), but there was no statistically significant difference between groups in the rate of disease progression or change in disability status.

### Systematic Reviews

A 2011 systematic review published evaluated the safety and efficacy of autologous HCT in patients with progressive MS refractory to conventional medical treatment. Eight case series met the inclusion criteria for the primary outcome of PFS, with a median follow-up of at least 2 years. An additional 6 studies were included for a summary of mortality and morbidity. For the 8 case series, there was substantial heterogeneity across studies. Most patients (77%) had secondary progressive MS, although studies also included those with primary progressive, progressive-relapsing, and relapse-remitting disease. Numbers of patients across studies ranged between 14 and 26. The studies differed in the types and intensities of conditioning regimens used prior to HCT, with 5 studies using an intermediate-intensity regimen and 3 using high-intensity regimens. All studies were rated as moderate quality. The estimated rate of long-term PFS of patients receiving intermediate-intensity conditioning regimen was 79.4% (95% CI, 69.9% to 86.5%) with a median follow-up of 39 months, while the estimate for patients who received a high-dose regimen was 44.6% (95% CI, 26.5% to 64.5%) at a median follow-up of 24 months. Of the 14 studies that reported on adverse events, 13 were case series; from these, 7 treatment-related deaths were recorded; 6 non-treatment-related deaths occurred, 5 associated with disease progression.

### Nonrandomized Studies

A 2012 study by Shevchenko et al reported the results of a prospective, open-label, single-center study that analyzed the safety and efficacy of autologous HCT with reduced-intensity conditioning regimen in 95 patients with different types of MS. Patients underwent early, conventional, and salvage/late transplantation. Efficacy was evaluated based on clinical and quality-of-life (QOL) outcomes. No transplantation-related deaths were observed. All patients, except 1, responded to treatment. At long-term follow-up (mean, 46 months), the overall clinical response in terms of disease improvement or stabilization was 80%. The estimated PFS at 5 years was 92% in the group after early transplant and 73% in the group after conventional/salvage transplant ( $p = 0.01$ ). No active, new, or enlarging lesions on MRI were found in patients without disease progression. All patients who did not have disease progression were off therapy throughout the posttransplantation period. HCT was accompanied by a significant improvement in QOL, with statistically significant changes in most QOL parameters ( $p < 0.05$ ). A 2015 subsequent publication

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

reported on 64 patients participating in this trial who had at least 36 months of follow-up (median, 62 months). (Another 35 patients had shorter follow-up and the remainder were lost to follow-up.) Thirty (47%) of the 64 patients improved at least 0.5 point on the EDSS score compared with baseline. Among the other patients, 29 (45%) were stable and 5 (7%) experienced worsening disease.

In 2012, Mancardi et al reported on 74 consecutive patients with MS treated using autologous HCT with an intermediate-intensity conditioning regimen in the period from 1996 to 2008. Thirty-six patients had secondary progressive disease and 25 had relapsing-remitting MS. Clinical and MRI outcomes were reported. Median follow-up was 48.3 months (range, 0.8-126 months). Two patients (2.7%) died from transplant-related causes. After 5 years, 66% of patients remained stable or improved. Among patients with a follow-up longer than 1 year, 8 (31%) of 25 subjects with a relapsing-remitting course had a 6- to 12-month confirmed EDSS score improvement greater than 1 point after HCT compared with 1 (3%) of 36 patients with a secondary progressive disease course ( $p=0.009$ ). Among the 18 cases with a follow-up longer than 7 years, 8 (44%) remained stable or had a sustained improvement, while 10 (56%), after an initial period of stabilization or improvement (median duration, 3.5 years), showed a slow disability progression.

A 2015 single-center case series by Burt et al reported on 151 patients, 123 with relapsing-remitting MS and 28 with secondary progressive MS. Patients were treated with nonmyeloablative HCT between 2003 and 2014. Six patients were not included in the outcome analysis. The remaining 145 patients were followed for a median of 2 years (range, 6 months to 5 years). There were no treatment-related deaths. The primary outcome was change in the EDSS score. A decrease of at least 1.0 point was considered significant improvement and an increase of at least 1.0 point was considered significant progression. There was statistically significant improvement in EDSS score for the group as a whole compared with the pretransplant mean score of 4.0, decreasing to a mean EDSS score of 2.5 at 3, 4, and 5 years. In post hoc analysis, patients most likely to have statistically significant improvements in EDSS score were those with relapsing-remitting MS, with duration of disease of 10 years or less, and those without sustained fever during HCT.

Several studies have focused on patients with aggressive MS. In 2011, Fassas et al reported the long-term results of a single-center study that investigated the effect of HCT in the treatment of MS. The authors reported, after a median follow-up period of 11 years (range, 2-15 years), on the clinical and MRI outcomes of 35 patients with aggressive MS treated with HCT. Disease PFS at 15 years was 44% for patients with active central nervous system disease and 10% for those without ( $p=0.01$ ); median time to progression was 11 years (range, 0-22 years) and 2 years (range, 0-6 years), respectively. Improvements by 0.5 to 5.5 (median, 1) EDSS points were observed in 16 cases, lasting for a median of 2 years. In 9 of these patients, EDSS scores did not progress above baseline scores. Two patients died, at 2 months and 2.5 years, from transplant-related complications. Gadolinium-enhancing lesions were significantly reduced after mobilization but were maximally and persistently diminished post-HCT.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

A 2014 multicenter case series by Burman et al reported on 48 patients with aggressive relapsing-remitting MS, defined as disease with high relapse frequency, and who failed conventional therapy. Patients underwent autologous HCT. At the 5-year follow-up, relapse-free survival was 87% and the EDSS score PFS (EDSS deterioration of <0.5 points) was 77%. The rate of disease-free survival (no relapses, no new MRI lesions, no EDSS score progression) was 68%.

In 2016, Atkins et al published a phase 2 trial investigating the use of immunoablation and autologous HCT for the treatment of aggressive MS. Inclusion criteria were: poor prognosis, ongoing disease activity, and EDSS score between 3.0 and 6.0. Twenty-four patients enrolled, and had a median follow-up of 6.7 years (range, 4-13 years). One patient died of transplant-related complications (hepatic necrosis following sepsis). The primary outcome (activity-free survival at 3 years after transplantation) was 70% (95% CI, 47% to 84%). During the extended follow-up period, without the use of disease-modifying drugs, no signs of central nervous system inflammation were detected clinically or radiologically. Clinical relapses did not occur among the 23 surviving patients in 179 patient-years of follow-up. Thirty-three percent of the patients experienced grade 2 toxic effects and 58% experienced grade 1 transplantation-related toxic effects.

Results from the High-Dose Immunosuppression and Autologous Transplantation for Multiple Sclerosis (HALT-MS) trial were published in 2017 by Nash et al. The trial evaluated 24 patients with MS who were treated with high-dose immunosuppression and autologous HCT. The median follow-up was 62 months (range, 12-72 months). Outcomes were PFS (91%; 90% CI, 75% to 97%), clinical relapse-free survival (87%; 90% CI, 69% to 95%), and MRI activity-free survival (86%; 90% CI, 68% to 95%). Patients experienced high rates of adverse events: 92% had grade 3 and 100% had grade 4 adverse events. The majority of adverse events occurred between the start of conditioning to day 29 in the trial.

### **Section Summary: Multiple Sclerosis**

Evidence for the use of HCT in patients with MS consists of an RCT and many single-arm studies. The RCT compared HCT (n=9) with mitoxantrone (n=12). The primary outcome was the number of new T2 lesions detected by MRI. The HCT group developed statistically fewer lesions than the mitoxantrone group. Outcomes in the single-arm studies included PFS, relapse-free survival, disease activity-free survival, disease stabilization, number of new lesions, and improvements in EDSS scores. While improvements were seen in all outcomes compared with baseline, there were no comparative treatments. Adverse event rates were high, and most studies reported treatment-related deaths.

### **Systemic Sclerosis/Scleroderma**

#### **Systematic Reviews**

In 2015, van Laar et al conducted a systematic review of evidence on the use of HCT for treating poor-prognosis systemic sclerosis. They identified 3 RCTs comparing HCT with the standard of care (cyclophosphamide): a phase 2 trial and a completed phase 3 trial, both of which are described in the Randomized Controlled Trial section, plus a phase 3 trial (Scleroderma: Cyclophosphamide or Transplantation [SCOT]). SCOT has been completed and results presented at a 2016 American College of

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

Rheumatology conference. Results have not been published at the time of this update. Reviewers concluded that there is evidence HCT can result in significant improvements in skin thickness and functional outcomes. However, HCT is associated with serious toxicities that can be fatal. Additional trials are needed to assess how to reduce toxicity and to determine which patients with scleroderma would benefit most from HCT.

A review in 2011 by Milanetti et al summarized 8 phase 1 and 2 clinical studies using autologous HCT to treat systemic sclerosis. The number of patients in each study ranged from 6 to 57. The proportion of patients across the studies achieving a 25% decrease in the Rodnan Skin Score (RSS) ranged from 60% to 100%. Pooled analyses were not conducted.

### Randomized Controlled Trials

Results of the Autologous Stem Cell Transplantation International Scleroderma (ASTIS) trial (ISRCTN54371254) were published in 2014. ASTIS was a phase 3 RCT conducted in 10 countries at 29 centers with access to an EBMT-registered transplant facility. A total of 156 patients were recruited between March 2001 and October 2009. Patients were eligible if they were between 18 and 65 years of age; had diffuse cutaneous systemic sclerosis according to American Rheumatism Association criteria, with maximum duration of 4 years; minimum modified Rodnan Skin Score (RSS) of 15 (range, 0-51; higher scores indicate more severe skin thickening); and involvement of heart, lungs, or kidneys. Patients were randomly allocated to receive high-dose chemotherapy (intravenous cyclophosphamide 200 mg/kg over 4 consecutive days and intravenous rabbit antithymocyte globulin 7.5 mg/kg total dose over 3 consecutive days) followed by CD34+ selected autologous HCT support (n=79) or 12 monthly treatments with intravenous pulsed cyclophosphamide (750 mg/m<sup>2</sup>). Median follow-up was 5.8 years (interquartile range, 4.1-7.8 years). The primary end point was event-free survival, defined as the time in days from randomization until the occurrence of death due to any cause or the development of persistent major organ failure (heart, lung, kidney). Main secondary end points included treatment-related mortality, toxicity, and disease-related changes in modified RSS, organ function, body weight, and QOL scores. The internal validity (risk of bias) of ASTIS was assessed according to the U.S. Preventive Services Task Force criteria for randomized trials. The study was rated as "poor" quality according to this framework because of 2 fatal flaws: outcome assessment was not masked to patients or assessors, and 18 (24%) of 75 of the control group discontinued intervention because of death, major organ failure, adverse events, or nonadherence. Furthermore, the trial design permitted crossover after the second year, but whether any patients did so and were analyzed as such is not mentioned. Finally, the authors reported that the use of unspecified concomitant medications or other supportive care measures were allowed at the discretion of the investigators, adding further uncertainty to the results.

Of the 53 primary end point events recorded, 22 were in the HCT group (19 deaths, 3 irreversible organ failures; 8 patients died of treatment-related causes in the first year, 9 of disease progression, 1 of cerebrovascular disease, 1 of malignancy) and 31 were in the control group (23 deaths, 8 irreversible organ failures [7 of whom died later]; 19 patients died of disease progression, 4 of cardiovascular disease, 5 of malignancy, 2 of other causes). The data showed patients treated with HCT experienced more events in the

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.





# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

first year but appeared to have better long-term event-free survival than the controls, with Kaplan-Meier curves for OS crossing at about 2 years after treatment with OS at that time estimated at 85%. According to the Kaplan-Meier curves, at 5 years, OS was an estimated 66% in the control group and an estimated 80% in the HCT group (p value unknown). Time-varying hazard ratios (modeled with a treatment by time interaction) for event-free survival were 0.35 (95% CI, 0.15 to 0.74) at 2 years and 0.34 (95% CI, 0.16 to 0.74) at 4 years, supporting a benefit of HCT compared with pulsed cyclophosphamide. Severe or life-threatening grade 3 or 4 adverse events were reported in 51 (63%) of the HCT group and 30 (37% by intention-to-treat,  $p=0.002$ ) of the control group.

An open-label, randomized, controlled phase 2 trial (ASSIST; 2011) evaluated the safety and efficacy of autologous nonmyeloablative HCT compared with the standard of care (cyclophosphamide). Nineteen consecutively enrolled patients less than 60 years of age with diffuse systemic sclerosis, modified RSS greater than 14, and organ involvement or restricted skin involvement (modified RSS,  $<14$ ) but coexistent pulmonary involvement were randomized 1:1 to HCT, intravenous cyclophosphamide 200 mg/kg, plus rabbit antithymocyte globulin or to intravenous cyclophosphamide 1.0 g/m<sup>2</sup> once per month for 6 months. The primary outcome was an improvement at 12 months, which was defined as a decrease in modified RSS ( $<25\%$  for those with initial modified RSS  $>14$ ) or an increase in forced vital capacity of more than 10%. Patients in the control group with disease progression ( $>25\%$  increase in modified RSS or decrease of  $>10\%$  in forced vital capacity) despite treatment with cyclophosphamide could switch to HCT 12 months after enrollment. No deaths occurred in either group during follow-up. Patients allocated to HCT ( $n=10$ ) improved at or before the 12-month follow-up compared with none of the 9 patients allocated to cyclophosphamide ( $p<0.001$ ). Treatment failure (ie, disease progression without interval improvement), occurred in 8 of 9 controls but did not occur in any of the 10 patients treated by HCT ( $p<0.001$ ). After long-term follow-up (mean, 2.6 years) of patients allocated to HCT, all but 2 patients had sustained improvement in modified RSS and forced vital capacity, with a longest follow-up of 60 months. Seven patients allocated to receive cyclophosphamide switched treatment groups at a mean of 14 months after enrollment and underwent HCT without complication; all improved after HCT. Four of these patients, followed for at least 1 year, had a mean (standard deviation [SD]) decrease in modified RSS from 27 (SD=15.5) to 15 (SD=7.4), an increase in forced vital capacity from 65% (20.6%) to 76% (26.5%), and an increase in total lung capacity from 81% (14.0%) to 88% (13.9%). Data for 11 patients with follow-up to 2 years after HCT suggested that the improvements in modified RSS ( $p<0.001$ ) and forced vital capacity ( $p<0.03$ ) persisted.

### Nonrandomized Studies

Vonk et al (2008) reported the long-term results of 28 patients with severe diffuse cutaneous systemic sclerosis who underwent autologous HCT from 1998 to 2004. There was 1 transplant-related death and 1 death due to progressive disease, leaving 26 patients for evaluation. After a median follow-up of 5.3 years (range, 1-7.5 years), 81% ( $n=21/26$ ) of the patients demonstrated a clinically beneficial response. Skin sclerosis was measured with a modified RSS, and a significant (ie,  $>25\%$ ) decrease (ie, improvement) was achieved in 19 of 26 patients after 1 year and in 15 of 16 after 5 years. At study baseline, 65% of patients had significant lung involvement; all pulmonary function parameters remained stable after transplant at 5- and 7-year follow-ups. Based on the World Health Organization Performance Status, which reflects the

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

effect of HCT on the combination of functional status, skin, lung, heart, and kidney involvement, the percentage of patients with a Performance Status score of 0 increased to 56% from 4% at baseline. Estimated survival at 5 years was 96.2% (95% CI, 89% to 100%) and at 7 years was 84.8% (95% CI, 70.2% to 100%); and event-free survival (survival without mortality, relapse, or progression of systemic sclerosis resulting in major organ dysfunction) was 64.3% (95% CI, 47.9% to 86%) at 5 years and 57.1% (95% CI, 39.3% to 83%) at 7 years. For comparison, an international meta-analysis published in 2005 estimated the 5-year mortality rate in patients with severe systemic sclerosis at 40%.

Nash et al (2007) reported on the long-term follow-up of 34 patients with diffuse cutaneous systemic sclerosis with significant visceral organ involvement who were enrolled in a multi-institutional pilot study between 1997 and 2005 and underwent autologous HCT. Of the 34 patients, 27 (79%) survived 1 year and were evaluable for response (there were 8 transplant-related deaths and 4 systemic sclerosis-related deaths). Of the 27 evaluable patients, 17 (63%) had sustained responses at a median follow-up of 4 years (range, 1-8 years). Skin biopsies showed a statistically significant decrease in dermal fibrosis compared with baseline ( $p < 0.001$ ) and, in general, lung, heart, and kidney function remained stable. Overall function as assessed in 25 patients using the Disability Index of the modified Health Assessment Questionnaire showed improvement in 19, and disease response was observed in the skin of 23 of 25 and lungs of 8 of 27 patients. Estimated OS and PFS rates were both 64% at 5 years.

Henes et al (2012) reported on 26 consecutive patients with systemic sclerosis scheduled for autologous HCT between 1997 and 2009. The main outcome variable was response to treatment (reduction of modified RSS by 25%) at 6 months. Secondary end points were transplant-related mortality and PFS. At 6 months, significant skin and lung function improvement assessed on the modified RSS was achieved in 78.3% of patients. Overall response rate was 91%, and some patients even improved after month 6. Three patients died between mobilization and conditioning treatment—two due to severe disease progression and one treatment-related. Seven patients relapsed during the 4.4 years of follow-up. PFS was 74%. Four patients died during follow-up, with the most frequent causes of death being pulmonary and cardiac complications of systemic sclerosis.

### **Section Summary: Systemic Sclerosis/Scleroderma**

Evidence for the use of HCT in patients with systemic sclerosis/scleroderma consists of 3 RCTs and nonrandomized studies. Two (one with 19 patients, the other with 156 patients) have published results, and reported statistical significant improvements in clinical outcomes (skin thickness, forced vital capacity). The larger trial (ASTIS) also reported improved OS. However, HCT can result in serious adverse events due to toxicity. The third RCT, completed and expected to be published soon, employed a different transplant regimen. Additional information on the best treatment regimen to reduce toxicity and long-term follow-up is still needed.

### **SYSTEMIC LUPUS ERYTHEMATOSUS**

Burt et al (2006) published results on the largest single-center series using HCT for SLE in the United States. Between 1997 through 2005, investigators enrolled 50 patients (mean age, 30 years, 43 women, 7

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

men) with SLE refractory to standard immunosuppressive therapies and either organ- or life-threatening visceral involvement in a single-arm trial. All subjects had at least 4 of 11 American College of Rheumatology criteria for SLE and required more than 20 mg/d of prednisone or its equivalent, despite the use of cyclophosphamide. Patients underwent autologous HCT following a lymphoablative conditioning regimen. Two patients died after mobilization, yielding a treatment-related mortality rate of 4% (2/50). After a mean follow-up of 29 months (range, 6 months to 7.5 years), the 5-year OS rate was 84%, and the probability of disease-free survival rate was 50%. Several parameters of SLE activity improved, including renal function, SLE Disease Activity Index score, antinuclear antibody, anti-double stranded DNA, complement C3 and C4 levels, and carbon monoxide diffusion lung capacity. The investigators suggested these results justified a randomized trial comparing immunosuppression plus autologous HCT with continued standard of care.

Song et al (2011) reported on the efficacy and toxicity of autologous HCT for 17 patients with SLE after 7 years follow-up. OS and PFS rates were used to assess the efficacy and toxicity levels of the treatment. The median follow-up was 89 months (range, 33-110 months). The probabilities of 7-year OS and PFS were 82.4% (SD=9.2%) and 64.7% (SD=11.6%), respectively. The principal adverse events included allergy, infection, elevated liver enzymes, bone pain, and heart failure. Two patients died, one due to severe pneumonia and the other due to heart failure at 33 and 64 months after transplantation, respectively. The authors concluded that their 7-year follow-up results suggested that autologous HCT was beneficial for SLE patients.

Leng et al (2017) reported on 24 patients with severe SLE who received high-dose immunosuppressive therapy and HCT. Patients were followed for 10 years. One patient died following treatment. At the 6-month follow-up, 2 patients had achieved partial remission, and 21 patients had achieved remission. At the 10-year follow-up, the OS rate was 86%; 16 patients remained in remission, 4 were lost to follow-up, 2 patients had died, and 1 patient had active disease.

### **Section Summary: Systemic Lupus Erythematosus**

Evidence for the use of autologous HCT to treat patients with SLE consists of several case series (total N=91 patients). A 4% treatment-related mortality rate was reported in 2 studies. High rates of remission were reported at 6 months, and at 2- to 10-year follow-ups. While HCT has shown beneficial effects on patients with SLE, further investigation of more patients is needed.

### **JUVENILE IDIOPATHIC OR RHEUMATOID ARTHRITIS**

A 2008 review article by Saccardi et al on HCT for autoimmune diseases has summarized the experience with juvenile idiopathic arthritis and rheumatoid arthritis as follows. More than 50 patients with juvenile idiopathic arthritis have been reported to the EBMT Registry. The largest cohort study initially used a single conditioning regimen and, thereafter, a modified protocol. Overall drug-free remission rate was approximately 50%. Some late relapses have been reported, and only partial correction of growth impairment has been seen. The frequency of HCT for rheumatoid arthritis has decreased significantly since

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

2000, due to the introduction of new biologic therapies. Most patients who have undergone HCT have had persistence or relapse of disease activity within 6 months of transplant.

### Section Summary: Juvenile Idiopathic or Rheumatoid Arthritis

Evidence for the use of HCT on patients with juvenile idiopathic arthritis consists of data from an EBMT Registry (N>50). Different conditioning regimens were used among the patients, with remission rates averaging 50%. However, relapse has been reported within 6 months in many cases, and new biologic therapies are available for these patients.

### CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

Several review articles have summarized experience with HCT in the treatment of chronic inflammatory demyelinating polyneuropathy. In general, the evidence includes a few case reports describing outcomes for autologous HCT in patients who failed standard treatments such as corticosteroids, intravenous immunoglobulins, and plasma exchange. While improvements were reported, some with long-term follow-up, the numbers of patients undergoing the procedure are small, and the potential for serious adverse events is a concern.

### Section Summary: Chronic Inflammatory Demyelinating Polyneuropathy

Evidence for the use of HCT to treat patients with chronic inflammatory demyelinating polyneuropathy consists of case reports. Additional investigations are needed due to the toxicity associated with this procedure.

## TYPE 1 DIABETES

### Systematic Reviews

In 2016, El-Badawy and El-Badri published a meta-analysis on the use of HCT to treat diabetes. The literature search, conducted through August 2015, identified 22 studies for inclusion. Fifteen of the studies (n=300 patients) involved patients with type 1 diabetes; 7 studies (n=224 patients) involved patients with type 2 diabetes. The quality of the selected studies was assessed using criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The following items were evaluated to determine the risk of bias: attrition, confounding measurement, intervention, performance, selection, and conflict of interest. The mean follow-up in the studies ranged from 6 to 48 months (median, 12 months). Comparisons of C-peptide levels and hemoglobin A<sub>1c</sub> levels after 12-month follow-up were calculated by type of diabetes (1 or 2) and source of stem cells (see Table 1). Adverse events were reported in 22% of the patients, with no reported mortality. Reviewers concluded that remission of diabetes is possible and safe with stem-cell therapy, patients with previously diagnosed ketoacidosis are not good candidates for HCT, and that early-stage patients may benefit more from HCT. Large-scale well-designed randomized studies considering stem-cell type, cell number, and infusion method is needed.

**Table 1. Standard Mean Differences From Baseline in C-Peptide and HbA<sub>1c</sub> Levels in Patients With Diabetes Treated With HCT After 12 Months of Follow-Up**

Diabetes	No. of	Patients	SMD (95% CI)	No. of	Patients	SMD (95% CI)
----------	--------	----------	--------------	--------	----------	--------------

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

Subgroups	Studies		C-Peptide	Studies		HbA <sub>1c</sub>
<b>Type 1</b>						
UCB	4	56	1.07 (0.67 to 1.48)	4	61	0.05 (-0.30 to 0.41)
UC-MSc	1	15	-0.91 (-1.67 to -0.16)	1	15	1.19 (0.41 to 1.98)
BM-HSC	4	97	-1.37 (-1.69 to -1.05)	3	96	3.87 (3.29 to 4.44)
BM-MSc	1	10	-1.18 (-2.15 to -0.22)	NA	NA	NA
IS-ADSc + BM-HSC	2	21	-1.01 (-1.73 to -0.30)	2	21	0.93 (0.27 to 1.59)
Total	12	199	-0.57 (-1.73 to -0.35)	10	193	1.09 (0.83 to 1.35)
<b>Type 2</b>						
UCB	1	2	-0.55 (-4.23 to 3.13)	1	2	0.73 (-3.83 to 5.29)
UC-MSc	1	22	-0.61 (-1.21 to 0.00)	1	22	0.93 (0.30 to 1.55)
PD-MSc	1	10	-0.38 (-1.27 to 0.50)	1	10	1.50 (0.49 to 2.53)
BM-MNC	2	41	-1.29 (-1.77 to -0.81)	4	107	1.16 (0.85 to 1.46)
Total	5	75	-0.93 (-1.27 to -0.58)	7	141	1.14 (0.88 to 1.40)

BM-HSC: bone marrow hematopoietic stem cells; BM-MNC: bone marrow mononuclear stem cells; BM-MSc: bone marrow mesenchymal stem cells; CI: confidence interval; HbA<sub>1c</sub>: hemoglobin A<sub>1c</sub>; HCT: hematopoietic cell transplantation; IS-ADSc: insulin secreting-adipose derived stem cells; NA: not applicable; PD-MSc: placenta-derived mesenchymal stem cells; SMD: standard mean difference; UCB: umbilical cord blood; UC-MSc: umbilical cord mesenchymal stem cells

### Case Series

Several case series evaluated autologous HCT in patients with new-onset type 1 diabetes; there were no published comparative studies. Although a substantial proportion of patients tended to become insulin-free after HCT, remission rates were high.

In 2016, Cantu-Rodriguez et al published a study of 16 patients with type 1 diabetes who received a less toxic conditioning regimen and transplantation. The outpatient procedures were completed without severe complications. At the 6-month follow-up, 3 (19%) were nonresponders, 6 (37%) partially independent from insulin, and 7 (44%) were completely independent of insulin. Hemoglobin A<sub>1c</sub> levels decreased by a mean of -2.3% in the insulin-independent group.

In 2015, Xiang et al published data on 128 patients ages 12 to 35 years who had been diagnosed with type 1 diabetes no more than 6 weeks before study enrollment. After a mean follow-up of 28.5 months (range, 15-38 months), 71 (55%) patients were considered to be insulin-free. These patients had a mean remission period of 14.2 months. The other 57 (45%) patients were insulin-dependent. The latter group included 27 patients with no response to treatment and another 30 patients who relapsed after a transient remission period. Adverse events included ketoacidosis and renal dysfunction (1 patient each); there was no transplant-related mortality. In multiple logistic regression analysis, factors independently associated with becoming insulin-free after autologous HCT were younger age at onset of diabetes, lower tumor necrosis factor  $\alpha$  levels, and higher fasting C-peptide levels.

A 2016 case series by Snarski et al reported on 24 patients with a diagnosis of type 1 diabetes who underwent autologous HCT. Mean age was 26.5 years (range, 18-34 years). After treatment, 20 (87%) of

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

23 patients went into diabetes remission, defined as being insulin-free with normoglycemia for at least 9.5 months. The median time of remission was 31 months (range, 9.5-80 months). Mean insulin doses remained significantly lower than baseline doses at 2 and 3 years, but the insulin doses returned to pre-HCT levels at years 4 and 5. Among 20 patients remaining in follow-up at the time of data analysis for publication, 4 (20%) remained insulin-free. Adverse events include neutropenic fever in 12 (50%) patients. There were 4 cases of sepsis, including a fatal case of *Pseudomonas aeruginosa* sepsis. There was also 1 case of pulmonary emphysema after insertion of a central venous catheter.

In 2009, Couri et al reported on the results of a prospective case series evaluating autologous HCT in 23 patients with type 1 diabetes (age range, 13-31 years) diagnosed in the 6 weeks before transplant based on clinical findings including hyperglycemia and confirmed by measurement of serum levels of antigliutamic acid decarboxylase antibodies. At a mean follow-up of 29.8 months (range, 7-58 months) after autologous nonmyeloablative HCT, C-peptide levels increased significantly (C-peptide measures islet cell mass, and an increase after HCT indicates preservation of islet cells), and most patients achieved insulin independence with good glycemic control. Twenty patients without previous ketoacidosis and not receiving corticosteroids during the preparative regimen became insulin-free. Twelve patients maintained insulin independence for a mean of 31 months (range, 14-52 months), and 8 patients relapsed and resumed low-dose insulin. In the continuously insulin-independent group, hemoglobin A<sub>1c</sub> levels were less than 7.0%. There was no transplant-related mortality.

### Section Summary: Type 1 Diabetes

Evidence for the use of HCT to treat diabetes consists of several case series and a meta-analysis of 22 studies. The meta-analysis revealed that HCT is more effective in patients with type 1 diabetes and when the treatment is administered soon after the diagnosis. Certain factors limit the conclusions that can be drawn about the overall effectiveness of HCT to treat diabetes; those factors are: heterogeneity in the stem-cell types, cell number infused, and infusion methods.

### OTHER AUTOIMMUNE DISEASES

Phase 2/3 protocols are being developed for Crohn disease. For the remaining autoimmune diseases (eg, immune cytopenias, relapsing polychondritis), sample sizes are too small to draw conclusions.

A case series of 7 patients with myasthenia gravis was reported by Bryant et al (2016). Using the Myasthenia Gravis Foundation of America clinical classification, all patients achieved complete stable remission, with follow-up from 29 to 149 months. The authors concluded that these positive long-term results warranted further investigation of HCT for patients with myasthenia gravis.

### Section Summary: Other Autoimmune Diseases

Evidence for the use of HCT for other autoimmune diseases consists of small retrospective studies. Information from larger prospective studies is needed.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

### **SUMMARY OF EVIDENCE**

For individuals with multiple sclerosis who receive hematopoietic cell transplantation (HCT), the evidence includes a RCT and several case series. Relevant outcomes are overall survival, health status measures, quality of life, and treatment-related mortality 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) 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 with systemic sclerosis/scleroderma who receive HCT, the evidence includes RCTs and observational studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. The results of the ASTIS trial (N=156) have suggested high-dose chemotherapy plus autologous HCT might 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 HCT recipients than for controls. A smaller RCT (N=19) found that the rate of improvement at 12 months was significantly higher in the HCT group than in the conventional therapy group. Data from these trials, however, are inconclusive, and additional studies are needed to confirm safety and efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic lupus erythematosus who receive HCT, the evidence includes case series. Relevant outcomes are overall survival, symptoms, quality of life, and treatment-related mortality and morbidity. Several case series (total N=91 patients) have been published. 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. Relevant outcomes are symptoms, quality of life, medication use, and treatment-related mortality and morbidity. The registry included 50 patients with juvenile idiopathic or rheumatoid arthritis. 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 chronic inflammatory demyelinating polyneuropathy who receive HCT, the evidence includes case reports. Relevant outcomes are overall survival, symptoms, health status measures, quality

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

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.

For individuals with type 1 diabetes who receive HCT, the evidence includes case series and a meta-analysis of 22 studies. Relevant outcomes are overall survival, symptoms, health status measures, quality of life, and treatment-related mortality and morbidity. While a substantial proportion of patients tended to become insulin-free after HCT, remission rates were still 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 other autoimmune diseases (eg, Crohn disease, immune cytopenias, relapsing polychondritis) who receive HCT, the evidence includes small retrospective studies. Relevant outcomes are 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.

### **References**

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual. "Hematopoietic Cell Transplantation for Autoimmune Diseases", 8.01.25, 07:2017.
2. Nikolov NP, Pavletic SZ. Technology insight: hematopoietic stem cell transplantation for systemic rheumatic disease. *Nat Clin Pract Rheumatol* 2008; 4(4):184-91.
3. Burt RK, Marmont A, Oyama Y et al. Randomized controlled trials of autologous hematopoietic stem cell transplantation for autoimmune diseases: the evolution from myeloablative to lymphoablative transplant regimens. *Arthritis Rheum* 2006; 54(12):3750-60.
4. Milanetti F, Abinun M, Voltarelli JC et al. Autologous hematopoietic stem cell transplantation for childhood autoimmune disease. *Pediatr Clin North Am* 2010; 57(1):239-71.
5. Sullivan KM, Muraro P, Tyndall A. Hematopoietic cell transplantation for autoimmune disease: updates from Europe and the United States. *Biol Blood Marrow Transplant* 2010; 16(1 suppl):S48-56.
6. Pasquini MC, Griffith LM, Arnold DL et al. Hematopoietic stem cell transplantation for multiple sclerosis: collaboration of the CIBMTR and EBMT to facilitate international clinical studies. *Biol Blood Marrow Transplant* 2010; 16(8):1076-83.
7. Reston JT, Uhl S, Treadwell JR et al. Autologous hematopoietic cell transplantation for multiple sclerosis: a systematic review. *Mult Scler* 2011; 17(2):204-13.
8. Atkins H. Hematopoietic SCT for the treatment of multiple sclerosis. *Bone Marrow Transplant* 2010; 45(12):1671-81.
9. Fagius J, Lundgren J, Oberg G. Early highly aggressive MS successfully treated by hematopoietic stem cell transplantation. *Mult Scler* 2009; 15(2):229-37.
10. Kimiskidis V, Sakellari I, Tsimourto V et al. Autologous stem-cell transplantation in malignant multiple sclerosis: a case with a favorable long-term outcome. *Mult Scler* 2008; 14(2):278-83.
11. Mancardi GL, Murialdo A, Rossi P et al. Autologous stem cell transplantation as rescue therapy in malignant forms of multiple sclerosis. *Mult Scler* 2005; 11(3):367-71.
12. Burt RK, Loh Y, Cohen B et al. Autologous non-myeloablative haematopoietic stem cell transplantation in relapsing-remitting multiple sclerosis: a phase I/II study. *Lancet Neurol* 2009; 8(3):244-53.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.





# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

13. Saccardi R, Kozak T, Bocelli-Tyndall C et al. Autologous stem cell transplantation for progressive multiple sclerosis: update of the European Group for Blood and Marrow Transplantation autoimmune diseases working party database. *Mult Scler* 2006; 12(6):814-23.
14. Fassas A, Kimiskidis VK, Sakellari I et al. Long-term results of stem cell transplantation for MS: a single-center experience. *Neurology* 2011; 76(12):1066-70.
15. Shevchenko JL, Kuznetsov AN, Ionova TI et al. Autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis. *Exp Hematol* 2012.
16. Mancardi GL, Sormani MP, Di Gioia M et al. Autologous haematopoietic stem cell transplantation with an intermediate intensity conditioning regimen in multiple sclerosis: the Italian multi-centre experience. *Mult Scler* 2012; 18(6):835-42.
17. Bowen JD, Kraft GH, Wundes A et al. Autologous hematopoietic cell transplantation following high-dose immunosuppressive therapy for advanced multiple sclerosis: long-term results. *Bone Marrow Transplant* 2012; 47(7):946-51.
18. Milanetti F, Bucha J, Testori A et al. Autologous hematopoietic stem cell transplantation for systemic sclerosis. *Curr Stem Cell Res Ther* 2011; 6(1):16-28.
19. van Laar JM, Farge D, Sont JK, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA*. Jun 25 2014;311(24):2490-2498. PMID 25058083
20. Burt RK, Shah SJ, Dill K et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomized phase 2 trial. *Lancet* 2011; 378(9790):498-506.
21. Vonk MC, Marjanovic Z, van den Hoogen FH et al. Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis. *Ann Rheum Dis* 2008; 67(1):98-104.
22. Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. *Am J Med* 2005; 118(1):2-10.
23. Nash RA, McSweeney PA, Crofford LJ et al. High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study. *Blood* 2007; 110(4):1388-96.
24. Henes JC, Schmalzing M, Vogel W et al. Optimization of autologous stem cell transplantation for systemic sclerosis -- a single-center longterm experience in 26 patients with severe organ manifestations. *J Rheumatol* 2012; 39(2):269-75.
25. Burt RK, Traynor A, Statkute L et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *JAMA* 2006; 295(5):527-35.
26. Saccardi R, Di GM, Bosi A. Haematopoietic stem cell transplantation for autoimmune disorders. *Curr Opin Hematol* 2008; 15(6):594-600.
27. Kazmi MA, Mahdi-Rogers M, Sanvito L. Chronic inflammatory demyelinating polyradiculoneuropathy: a role for haematopoietic stem cell transplantation? *Autoimmunity* 2008; 41(8):611-5.
28. Lehmann HC, Hughes RA, Hartung HP. Treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *Handb Clin Neurol* 2013; 115:415-27.
29. Peltier AC, Donofrio PD. Chronic inflammatory demyelinating polyradiculoneuropathy: from bench to bedside. *Semin Neurol* 2012; 32(3):187-95.
30. Couri CE, Oliveira MC, Stracieri AB et al. C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus. *JAMA* 2009; 301(15):1573-9.
31. Tyndall A, Gratwohl A. Adult stem cell transplantation in autoimmune disease. *Curr Opin Hematol* 2009; 16(4):285-91.
32. Khanna D, Georges GE, Couriel DR. Autologous hematopoietic stem cell therapy in severe systemic sclerosis: ready for clinical practice? *JAMA*. Jun 25 2014;311(24):2485-2487. PMID 25058081
33. Nash RA, Hutton GJ, Racke MK, et al. High-dose immunosuppressive therapy and autologous HCT for relapsing-remitting MS. *Neurology*. Feb 28 2017;88(9):842-852. PMID 28148635
34. van Laar JM, Naraghi K, Tyndall A. Haematopoietic stem cell transplantation for poor-prognosis systemic sclerosis. *Rheumatology (Oxford)*. Dec 2015;54(12):2126-2133. PMID 25953700
35. Milanetti F, Bucha J, Testori A, et al. Autologous hematopoietic stem cell transplantation for systemic sclerosis. *Curr Stem Cell Res Ther*. Mar 2011;6(1):16-28. PMID 20955159
36. Saccardi R, DiGioia M, Bosi A. Haematopoietic stem cell transplantation for autoimmune disorders. *Curr Opin Hematol*. Nov 2008;15(6):594-600. PMID 18832930
37. Cantu-Rodriguez OG, Lavallo-Gonzalez F, Herrera-Rojas MA, et al. Long-term insulin independence in type 1 diabetes mellitus using a simplified autologous stem cell transplant. *J Clin Endocrinol Metab*. May 2016;101(5):2141-2148. PMID 26859103

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050  
 Original Effective Date: 01/28/2002  
 Current Effective Date: 12/20/2017

38. Xiang H, Chen H, Li F, et al. Predictive factors for prolonged remission after autologous hematopoietic stem cell transplantation in young patients with type 1 diabetes mellitus. *Cytotherapy*. Nov 2015;17(11):1638-1645. PMID 26318272
39. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology*. Jul 26 2016;87(4):419-425. PMID 27358333
40. Alexander T, Bondanza A, Muraro PA, et al. SCT for severe autoimmune diseases: consensus guidelines of the European Society for Blood and Marrow Transplantation for immune monitoring and biobanking. *Bone Marrow Transplant*. Feb 2015;50(2):173-180. PMID 25387090

### **Policy History**

Original Effective Date:	01/28/2002
Current Effective Date:	12/20/2017
12/06/2001	Medical Policy Committee review
01/28/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review
06/28/2004	Managed Care Advisory Council approval. Format revision. No substance change to policy.
06/07/2006	Medical Director review
06/21/2006	Medical Policy Committee approval. Format revisions, FDA/Governmental, Rationale/Source. Coverage eligibility unchanged.
08/06/2008	Medical Director review
08/20/2008	Medical Policy Committee approval. No change to coverage eligibility.
08/06/2009	Medical Policy Committee approval
08/26/2009	Medical Policy Implementation Committee approval. No change to coverage eligibility. Title changed.
07/01/2010	Medical Policy Committee approval
07/21/2010	Medical Policy Implementation Committee approval. No change to coverage eligibility.
07/07/2011	Medical Policy Committee approval
07/20/2011	Medical Policy Implementation Committee approval. Added indications of juvenile idiopathic arthritis and diabetes mellitus to policy statement as investigational.
06/28/2012	Medical Policy Committee review
07/27/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding update
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. Chronic inflammatory demyelinating polyneuropathy added as investigational.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050  
 Original Effective Date: 01/28/2002  
 Current Effective Date: 12/20/2017

12/20/2017 Medical Policy Implementation Committee approval. Coverage eligibility unchanged. The word stem removed from title and body of policy.  
 06/13/2018 Coding update  
 Next Scheduled Review Date: 12/2018

### **Coding**

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	E08.3211-E08.3299 E08.3311-E08.3399 E08.3411-E08.3499 E08.3511-E08.3599
	E08.37X1-E08.37X9 E09.3211-E09.3299 E09.3311-E09.3399 E09.3411-E09.3499
	E09.3511-E09.3519 E09.3521-E09.3599 E09.37X1-E09.37X9 E10.10-E10.29
	E10.311-E10.319 E10.3211-E10.3299 E10.3311-E10.3399 E10.3411-E10.3499
	E10.3511-E10.3599 E10.36-E10.39 E10.37X1-E10.37X9 E10.40-E10.49
	E10.51-E10.59 E10.610-E10.649 E10.65-E10.9 E11.00-E11.01
	E11.21-E11.29 E11.311-E11.319 E11.3211-E11.3299 E11.3311-E11.3399
	E11.3411-E11.3499 E11.3511-E11.3599 E11.36-E11.39 E11.37X1-E11.37X9
	E11.40-E11.49 E11.51-E11.59 E11.610-E11.649 E11.65-E11.9
	E13.00-E13.29 E13.311-E13.359 E13.3211-E13.3399 E13.3411-E13.3499

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



# Louisiana

## Hematopoietic Cell Transplantation for Autoimmune Diseases

Policy # 00050

Original Effective Date: 01/28/2002

Current Effective Date: 12/20/2017

E13.3511-E13.3599	E13.36-E13.39	E13.37X1-E13.37X9	E13.40-E13.49
E13.51-E13.59	E13.610-E13.618	E13.620-E13.628	E13.630-E13.638
E13.641-E13.649	E13.65-E13.69	E13.8-E13.9	G35
M05.00-M05.079	M05.09-M05.10	M05.111-M05.179	M05.19-M05.20
M05.211-M05.279	M05.29-M05.30	M05.311-M05.379	M05.39
M05.60	M05.611-M05.679	M05.69	M06.1
M06.4	M08.00	M08.011-M08.079	M08.08-M08.09
M08.20	M08.211-M08.279	M08.28-M08.29	M08.3
M08.40	M08.411-M08.479	M08.48	M08.80
M08.811-M08.879	M08.88-M08.90	M08.911-M08.979	M08.98-M08.99
M12.00	M12.011-M12.079	M12.08-M12.09	M32.0
M32.10-M32.19	M32.8-M32.9	M34.0-M34.2	M34.81-M34.89
M34.9			

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2017 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.