Anthem

Medical Policy

Subject: Hematopoietic Stem Cell Transplantation for Diabetes Mellitus
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Description/Scope

This document addresses the use of hematopoietic stem cell transplantation to reconstitute the immune system as a treatment of diabetes mellitus (DM).

Position Statement

Investigational and Not Medically Necessary:

Autologous or allogeneic (ablative and non-myeloablative) hematopoietic stem cell transplantation is considered**investigational and not medically necessary** as a treatment of diabetes mellitus.

Rationale

Type 1 diabetes mellitus is a result of cell-mediated autoimmune destruction of pancreatic beta cells. Many clinical trials are investigating different treatment modalities to restore and maintain sufficient glucose control to avoid the detrimental effects of inadequate glucose metabolism. Pancreas transplant and islet cell transplantation to replace insulin producing beta cells are hindered by the limited supply of organs. Additionally, transplanted islet cells frequently succumb to continued destruction by the underlying host immune system.

Animal models suggest that immune suppression in newly diagnosed type 1 diabetes prevents further loss of insulin production (Burt, 2002). Early human studies demonstrated that various immune blocking therapies (prednisone, azathioprine, cyclosporine) may produce limited and short-term improvement in C-peptide levels, but these effects were not maintained after immunosuppression was discontinued (Canadian-European Randomized Control Trial Group, 1988). In addition, the Diabetes Control and Complications Trial (DCCT, 1998) showed that individuals with a larger beta cell reserve have a slower decline in C-peptide levels and fewer microvascular complications than individuals with low or undetectable C-peptide concentrations. As a result, beta cell preservation is felt to be an important target in the management of type 1 diabetes mellitus and in the prevention of its complications.

Burt and colleagues (2002) proposed application of hematopoietic stem cell transplantation to treat diabetes as an autoimmune disorder. It was proposed that administration of immune ablative therapy might induce tolerance to auto-antigens and promote islet cell regeneration. In theory, hematopoietic stem cells would serve as progenitor cells for the immune system as well as minimizing the duration and complications of myelosuppression.

In an attempt to moderate the immune destruction of pancreatic beta cells in newly diagnosed type 1 diabetes mellitus (DM), investigators in Brazil (Voltarelli, 2007) reported a small phase I/II trial using high-dose immunosuppression followed by autologous non-myeloablative hematopoietic stem cell transplantation (AHST) in 15 subjects. Couri (2009) provided an extended report of the original participants and an additional 8 for a total of 23 participants with a mean follow-up of 29.8 months (range 7-58 months). The subjects included in this study were aged 12 to 31 years (mean 18.4 years) with a diagnosis of type 1 DM within the previous 6 weeks. In this study, hematopoietic stem cells were mobilized with cyclophosphamide ($2.0g/m^2$) and granulocyte colony-stimulating factor. The stem cells were injected after conditioning with cyclophosphamide (200mg/kg) and rabbit antithymocyte globulin. The primary endpoints (Voltarelli, 2007) were transplant morbidity and mortality and the changes in exogenous insulin requirements. Secondary endpoints were levels of hemoglobin A_{1C}, C-peptide levels and anti-glutamic acid decarboxylase (anti-GAD) antibody titers. Anti-GAD antibodies are auto-antibodies directed against islet cell antigen. In the extension study (Couri, 2009), the primary outcome measure was C-peptide levels during the mixed-meal tolerance test, before and at different times following transplantation. The pre-transplant mean exogenous insulin requirement for all participants was 0.38 IU/kg per day. Statistical differences in anti-GAD antibodies were noted between the pre-transplant level of 31.8 U/mL and 12.5 U/mL at 6 months following therapy. There were no significant differences in anti-GAD antibodies at other time frames (Voltarelli, 2007).

In the extension study (range 7-58 months) 12 participants attained continuous insulin freedom for a mean of 31 months. The mean pre-transplant HbA_{1C} was 8% and decreased significantly ($p<0.001$) at 3, 12, 24, 36 and 48 months to 5.4%, 5.7%, 5.7%, 5.5% and 6.0%, respectively. Mean area under the curve (AUC) C-peptide levels increased from 225.0 [75.2] ng/mL per 2 hours to 785.4 [90.3] ng/mL per 2 hours ($p<0.001$) at 24 months, and 728.1 [144.4] ng/mL per 2 hours ($p=0.001$) at 36 months (Couri, 2009).

Additionally, for a mean of 17.7 months, 8 participants achieved intermittent freedom from insulin, but relapsed and resumed low-dose insulin therapy. Mean pre-transplantation (AUC) C-peptide level was 148.9 [75.2] ng/mL per 2 hours. It increased after transplantation to 546.8 [96.9] ng/mL per 2 hours ($p=0.001$) at 36 months and 413.9 [124.7] ng/mL per 2 hours at 48 months (Couri, 2009).

Of note, the first participant treated in this study had a low C-peptide level of 0.4 ng/mL at baseline, which did not increase after 1 year. In this participant, insulin requirements progressively increased to doses 250% more than baseline requirements. This participant was lost to follow-up at 1 year. The investigators reported the study protocol was then modified, and the initial participant's results were not included. Three participants did not achieve any freedom from insulin, and HbA_{1C} levels did not decrease below 7% despite increasing insulin therapy. Transplant-related complications were reported in all participants with a majority experiencing febrile neutropenia and alopecia. Two serious infectious complications (bilateral pneumonia) were recorded. There were no deaths. During long-term follow-up, 3 participants developed endocrine disorders and 9 reported oligospermia (Couri, 2009; Voltarelli, 2007).

Although this study involved a highly selected group of participants, early results suggest that islet cell tolerance may be potentially re-induced with high dose immunosuppression followed by AHST. However, the evidence at this point is insufficient to establish the long-term safety and durable efficacy of this therapy in the treatment of type 1 DM. Further study in randomized, controlled trials is needed to establish a role of this treatment in changing the natural history of type 1 DM. At this time, there is one phase I/II and one phase II clinical trial recruiting individuals for autologous hematopoietic stem cell transplantation (HSCT) for type 1 DM. For evaluation of the efficacy of autologous HSCT for type 2 DM, there is one ongoing phase II and one Phase II/III clinical trial recruiting participants.

A published study by Bhansali and colleagues (2009) provides the first prospective review of participants undergoing autologous bone marrow-derived stem cell transplantation (SCT) for type 2 DM, represented by progressive and inexorable *B*-cell dysfunction. The pilot trial consisted of 10 participants (8 men, 2 women, age 50-68 years) diagnosed with "type 2 DM for greater than 5 years, failure of triple oral antidiabetic drugs, currently on insulin (greater than or equal to 0.7 U/kg/day) at least for 1 year, and glutamic acid decarboxylase antibody negative were included." Ten participants underwent SCT with a reported 7 (70%) participants achieving a reduction in insulin requirement by greater than or equal to 50%, while the remaining 3 participants were categorized as nonresponders. As a result, post SCT there was a reduction in the demand for insulin with mean 41.2 units/ day (59%) (p=0.007). The authors concluded:

> This study shows that SCT is an effective and safe option of *B*-cell regeneration leading to reduction in insulin requirement in patients with type 2 DM requiring high doses of insulin. However, further large-scale and long-term studies are required to fully substantiate the role of SCT in the management of type 2 DM.

In 2018, Gu and colleagues reported findings from a phase II prospective, parallel-assigned, non-randomized trial (NCT00807651) that evaluated the safety and efficacy of AHSCT therapy in 40 participants with type 1 diabetes (T1D), 20 of whom received AHSCT therapy and 20 who were treated with insulin injections. Of the participants enrolled, 14 (70%) of the AHSCT group became insulin-dependent for 1.5 to 48 months compared to 1 participant in the insulin group. A total of 11 AHSCT participants relapsed within a median time of 19.5 (range 5.5 -1) months and resumed insulin. "C-peptide levels increased significantly at 3 months in both groups and later decreased, with the insulin group, showing more rapid deterioration." In the AHSCT group most of the adverse events were identified as transplant-related complications. In summary, the authors concluded that "because of high relapse rate, more information on longer-term outcomes is needed before AHSCT can be routinely considered for T1D patients".

Madani and colleagues (2022) conducted a systematic review and meta-analysis of HSCT for treatment of T1D, alone or in combination with mesenchymal stem cell transplantation. A total of 21 studies using HSCT alone were included, involving 491 individuals with T1D. Most of these clinical trials were single arm. There was some evidence that HSCT was associated with improved beta cell function: an insulin-free period (from 1 to 80 months) was experienced by 168 subjects (34.2%), and 332 (67.6%) had some reduction in total daily dose of insulin. However, heterogeneity in the HSCT studies was high, as judged by I^2 statistics of 79-98%, suggesting that there were significant inconsistencies in the studies that may affect the results. Heterogeneity may be due to different follow-up periods in these studies (ranging from 3 months to 5 years), individual nutrition, exercise, weight and stem cell dose. In addition, HCST with conditioning using granulocyte colony stimulating factor and cyclophosphamide was suggested to not be safe due to potential severe adverse events and mortality. Overall, the authors concluded that well-designed randomized clinical trials are needed to clarify the efficacy of HSCT in treating T1D.

There is insufficient evidence in the published peer-reviewed literature to support the use of hematopoietic stem cell transplantation to treat diabetes mellitus.

Background/Overview

According to the Centers for Disease Control and Prevention, there was an estimated 34.2 million (10.5%) of the U.S. population affected by diabetes mellitus in 2018. Diabetes mellitus, the 7th leading cause of death in the U.S., is a chronic condition marked by impaired metabolism of carbohydrate, protein and fat (CDC, 2020). The underlying problem in diabetes is in the production or utilization of insulin, the hormone secreted by the pancreas that controls the level of blood sugar by regulating the transfer of glucose from the blood into the cells. Diabetes mellitus, if poorly controlled, can cause cardiovascular disease, retinal damage that could lead to blindness, damage to the peripheral nerves, and injury to the kidneys. Management of diabetes mellitus involves attempting to keep the blood sugar in normal ranges without causing potentially dangerous hypoglycemia, or low blood sugar.

There are three major types of diabetes:

- Type 1 diabetes, formerly known as Juvenile Diabetes, is a condition where the body does not produce insulin, requiring the injection of insulin from other sources in order to maintain normal blood glucose levels. Approximately 5% to 10% of all diagnosed cases of diabetes are type 1. Although the onset can occur at any time, it usually affects children and young adults (Centers for Disease Control and Prevention [CDC]).
- Type 2 diabetes is a condition where the body's cells do not effectively use the insulin that is present in the blood and/or there is a progressive inability to produce adequate levels of insulin. Approximately 90-95% of individuals with diabetes are type 2, making this the most common form of diabetes.
- Gestational diabetes is a condition where blood glucose levels become elevated during pregnancy in women who normally do not have blood sugar problems. This type of diabetes affects about 4% of all pregnant women and the cause remains unknown. In the majority of cases, there is a return to normal blood glucose levels after delivery.

Type 1 diabetes mellitus (DM) occurs as a result of an autoimmune attack on insulin producing pancreas beta cells. Type 1 diabetics are dependent on exogenous insulin to maintain control of glucose levels.

Hematopoietic stem cell transplant for diabetes includes the use of high dose chemotherapy (HDC) or immunosuppressive agents. Bone marrow ablation is the most significant side effect of HDC. As a result, HDC is accompanied by a re-infusion of hematopoietic stem cells, which are primitive cells capable of replication and formation into mature blood cells, in order to repopulate the marrow. The potential donors of stem cells include:

1. Autologous - Stem cells can be harvested from the individual's own bone marrow prior to the cytotoxic therapy
2. Allogeneic - Stem cells harvested from a histocompatible donor

Donor stem cells, either autologous or allogeneic, can be collected from either the bone marrow or the peripheral blood. Stem cells may be harvested from the peripheral blood using a pheresis procedure. To increase the number of stem cells in the peripheral circulation, donors may be pretreated with a course of chemotherapy or hematopoietic growth factors, or both.

In addition, blood harvested from the umbilical cord and placenta shortly after delivery of neonates contains stem and progenitor cells. Although cord blood is an allogeneic source, these stem cells are antigenically "naïve" and thus, are associated with a lower incidence of rejection or graft versus host disease.

The most appropriate stem cell source for a particular individual depends upon his or her disease, treatment history, and the availability of a compatible donor. The most appropriate source of stem cells for each individual must balance the risks of graft failure in autologous procedures, the risks of graft rejection, and graft versus host disease in allogeneic procedures.

While some hematopoietic stem cell transplant protocols can be administered on an outpatient basis, an inpatient stay may be required.

While the intensity of the regimens used for conditioning in conventional HDC varies, collectively they have been termed

"myeloablative." Several less intense conditioning regimens have been developed recently and rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells. These regimens, collectively termed "non-myeloablative," also vary in intensity with substantial overlap between the ranges for "myeloablative" and "non-myeloablative" regimens. Studies have shown that donor allogeneic stem cells can engraft in recipients using less-intensive conditioning regimens that are sufficiently immunosuppressive to permit graft-host tolerance. Non-myeloablative allogeneic transplants also referred to as "mini-transplant" or "reduced intensity conditioning (RIC) transplant," are thought to be potentially as effective as conventional HDC followed by an allogeneic stem cell transplantation (AlloSCT), but with decreased morbidity and mortality related to the less intense non-myeloablative chemotherapy conditioning regimen.

Definitions

Ablative: A very high dose of a treatment, calculated to kill a tumor.

Blood glucose: A sugar that is present in the bloodstream.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull; this tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

C-peptide: A substance released by the pancreas in equal amounts as insulin.

Chemotherapy: Medical treatment of a disease, particularly cancer, with drugs or other chemicals; chemotherapy may vary by disease and stage.

Cytotoxic: Destructive to cells.

Glucose: A form of sugar required for proper functioning of the body.

Hemoglobin A1C: A test to measure the average blood glucose level over the previous 2-3 months; amount of glucose attached to the red blood cells.

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to re-populate the bone marrow.

High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

Hyperglycemia: Blood glucose levels that are higher than the normal range.

Hypoglycemia: Blood glucose levels that are lower than the normal range.

Insulin: A substance normally produced by the body that takes glucose from the blood and makes glucose usable by the cells of the body.

Non-myeloablative chemotherapy: A less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:

CPT	
38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207-38215	Transplant preparation of hematopoietic progenitor cells [includes codes 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215]
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38243	Hematopoietic progenitor cell (HPC); HPC boost
HCPCS	
S2142	Cord blood-derived stem cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage, marrow ablative therapy, drugs, supplies, hospitalization with outpatient follow-up, medical/surgical, diagnostic, emergency, and rehabilitative services, and the number of days of pre- and post-transplant care in the global definition
ICD-10 Procedure	
	Autologous transplantation
30233G0-30243G0	Transfusion of autologous bone marrow into peripheral or central vein, percutaneous approach [includes codes 30233G0, 30243G0]
30233Y0-30243Y0	Transfusion of autologous hematopoietic stem cells into peripheral or central vein, percutaneous approach [includes codes 30233Y0, 30243Y0]
	Allogeneic transplantation

30233G2-30243G4	Transfusion of allogeneic bone marrow, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233G2, 30233G3, 30233G4, 30243G2, 30243G3, 30243G4]
30233U2-30243U4	Transfusion of allogeneic T-cell depleted hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233U2, 30233U3, 30233U4, 30243U2, 30243U3, 30243U4]
30233X2-30243X4	Transfusion of allogeneic cord blood stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233X2, 30233X3, 30233X4, 30243X2, 30243X3, 30243X4]
30233Y2-30243Y4	Transfusion of allogeneic hematopoietic stem cells, related, unrelated or unspecified into peripheral or central vein, percutaneous approach [includes codes 30233Y2, 30233Y3, 30233Y4, 30243Y2, 30243Y3, 30243Y4]
	Pheresis
6A550ZV	Pheresis of hematopoietic stem cells, single
6A551ZV	Pheresis of hematopoietic stem cells, multiple

ICD-10 Diagnosis

E08.00-E08.9	Diabetes mellitus due to underlying condition
E09.00-E09.9	Drug or chemical induced diabetes mellitus
E10.10-E10.9	Type 1 diabetes mellitus
E11.00-E11.9	Type 2 diabetes mellitus
E13.00-E13.9	Other specified diabetes mellitus

References

Peer Reviewed Publications:

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2. Bhansali A, Upreti V, Khandelwal N, et al. Efficacy of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus. Stem Cells Dev. 2009; 18(10):1407-1416.
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10. Madani S, Amanzadi M, Aghayan HR, et al. Investigating the safety and efficacy of hematopoietic and mesenchymal stem cell transplantation for treatment of T1DM: a systematic review and meta-analysis. Syst Rev. 2022; 11(1):82.
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Government Agency, Medical Society, and Other Authoritative Publications:

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3. National Cancer Institute. Blood-Forming Stem Cell Transplants. Reviewed August 12, 2013. Available at: http://www.cancer.gov/cancertopics/factsheet/Therapy/bone-marrow-transplant. Accessed on September 25, 2023.
4. National Library of Medicine. Clinical Trials. Available at:http://clinicaltrials.gov/. Accessed on September 25, 2023.

Websites for Additional Information

1. American Diabetes Association available at:http://www.diabetes.org/. Accessed on September 25, 2023.
2. Centers for Disease Control and Prevention. Diabetes and Prediabetes. Reviewed September 6, 2022. Available at: https://www.cdc.gov/chronicdisease/resources/publications/factsheets/diabetes-prediabetes.htm. Accessed on September 25, 2023.
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Peripheral Blood Stem Cell
Stem Cell Support (SCS)
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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated References and Websites for Additional Information sections.
Reviewed	11/10/2022	MPTAC review. Updated Rationale, References and Websites sections.
Reviewed	11/11/2021	MPTAC review. Updated Rationale, References and Websites sections.
	10/01/2021	Updated Coding section with 10/01/2021 ICD-10-PCS changes; removed open approach codes deleted 09/30/2021.
Reviewed	11/05/2020	MPTAC review. Updated Rationale, Background, References and Websites sections.
Reviewed	11/07/2019	MPTAC review. Updated Rationale, References and Websites sections.
	10/01/2019	Updated Coding section with 10/01/2019 ICD-10-PCS changes; added 30230U2-30243U4; removed 30250G0-30263G1, 30250X1-30263Y1 deleted 09/30/2019.
Reviewed	11/08/2018	MPTAC review.
Reviewed	10/31/2018	Hematology/Oncology Subcommittee review. Updated Rationale, References and Websites sections.
Reviewed	11/02/2017	MPTAC review.
Reviewed	11/01/2017	Hematology/Oncology Subcommittee review. The document header wording updated from “Current Effective Date” to “Publish Date.” Updated Rationale, Background, References and Websites sections.
Reviewed	11/03/2016	MPTAC review.
Reviewed	11/02/2016	Hematology/Oncology Subcommittee review. Updated Rationale, Background, References and Websites sections.
	10/01/2016	Updated Coding section with 10/01/2016 ICD-10-PCS procedure code changes.
Reviewed	11/05/2015	MPTAC review.
Reviewed	11/04/2015	Hematology/Oncology Subcommittee review. Updated References and Websites sections. Removed ICD-9 codes from Coding section.
Reviewed	11/13/2014	MPTAC review.
Reviewed	11/12/2014	Hematology/Oncology Subcommittee review. Updated References and Websites.
Reviewed	11/14/2013	MPTAC review.
Reviewed	11/13/2013	Hematology/Oncology Subcommittee review. Updated Rationale, Background, References and Websites.
Reviewed	11/08/2012	MPTAC review.
Reviewed	11/07/2012	Hematology/Oncology Subcommittee review. Updated Background and Websites. Updated Coding section with 01/01/2013 CPT changes.
Reviewed	11/17/2011	MPTAC review.
Reviewed	11/16/2011	Hematology/Oncology Subcommittee review. Updated Background, References and Websites. Updated Coding section with 01/01/2012 CPT changes.
Reviewed	11/18/2010	MPTAC review.
Reviewed	11/17/2010	Hematology/Oncology Subcommittee review. Change title to: *Hematopoietic Stem Cell Transplantation for Diabetes Mellitus.* Updated Rationale, Definitions, Index, References and Websites.
Reviewed	11/19/2009	MPTAC review.
Reviewed	11/18/2009	Hematology/Oncology Subcommittee review. Updated rationale, references and websites.
Reviewed	11/20/2008	MPTAC review.
Reviewed	11/19/2008	Hematology/Oncology Subcommittee review. Updated rationale, references and websites.
	10/01/2008	Updated Coding section with 10/01/2008 ICD-9 changes.
	01/01/2008	Updated Coding section with 01/01/2008 HCPCS changes; removed HCPCS G0267 deleted 12/31/2007.
New	11/29/2007	MPTAC review.
New	11/28/2007	Hematology/Oncology Subcommittee review. Initial document development.

Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.