Protocol

Hematopoietic Cell Transplantation for Autoimmune Diseases

(80125)

Medical Benefit		**Effective Date**: 04/01/14	**Next Review Date**: 11/19
Preauthorization	Yes	**Review Dates**: 04/07, 05/08, 01/10, 01/11, 01/12, 01/13, 01/14, 11/14, 11/15, 11/16, 11/17, 11/18	

Preauthorization is required and must be obtained through Case Management.

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

Populations	Interventions	Comparators	Outcomes
Individuals: • With multiple sclerosis	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With systemic sclerosis/ scleroderma	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With systemic lupus erythematosus	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With juvenile idiopathic or rheumatoid arthritis	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy • Biologic therapy	Relevant outcomes include: • Overall survival • Symptoms • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With chronic inflammatory demyelinating polyneuropathy	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With type 1 diabetes	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With other autoimmune diseases (e.g., Crohn disease, immune cytopenias, relapsing polychondritis)	Interventions of interest are: • Hematopoietic cell transplantation	Comparators of interest are: • Conventional medication therapy	Relevant outcomes include: • Overall survival • Symptoms • Health status measures • Quality of life • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

Most patients with autoimmune disorders respond to conventional drug therapies; however, conventional drug therapies are not curative—and a proportion of patients suffer from autoimmune diseases that range from the severe to the recalcitrant to the rapidly progressive. It is in this group of patients with severe autoimmune disease that alternative therapies have been sought, including hematopoietic cell transplantation (HCT).

SUMMARY OF EVIDENCE

For individuals with multiple sclerosis who receive HCT, the evidence includes a randomized controlled trial (RCT) and several case series. 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) reporting on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with systemic sclerosis/scleroderma who receive HCT, the evidence includes 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 five-year

survival rate of 84% and the probability of disease-free survival was 50%. Additional data are needed from controlled studies to demonstrate efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with juvenile idiopathic or rheumatoid arthritis who receive HCT, the evidence includes registry data. Relevant outcomes are overall survival, symptoms, quality of life, 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 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 high. A 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 (e.g., 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.

POLICY

Autologous or allogeneic hematopoietic cell transplantation is considered **investigational** as a treatment of autoimmune diseases including, but not limited to, the following:

- multiple sclerosis
- systemic sclerosis/scleroderma
- systemic lupus erythematosus
- juvenile idiopathic or rheumatoid arthritis
- chronic inflammatory demyelinating polyneuropathy
- type 1 diabetes.

MEDICARE ADVANTAGE

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

BACKGROUND

AUTOIMMUNE DISEASES

Autoimmune diseases represent a heterogeneous group of immune-mediated disorders, including multiple sclerosis, systemic sclerosis/scleroderma, systemic lupus erythematosus, rheumatoid arthritis, and chronic immune demyelinating polyneuropathy. The National Institutes of Health has estimated that 5% to 8% of Americans have an autoimmune disorder.

The pathogenesis of autoimmune diseases is not well understood, but it appears to involve underlying genetic susceptibility and environmental factors that lead to loss of self-tolerance, culminating in tissue damage by the patient's own immune system (T-cells).

Treatment

Immune suppression is a common treatment strategy for many of these diseases, particularly the rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, scleroderma). Most patients with autoimmune disorders respond to conventional therapies, which consist of anti-inflammatory agents, immunosuppressants, and immunomodulating drugs; however, conventional drug therapies are not curative, and a proportion of patients suffer from autoimmune diseases that range from severe to recalcitrant to rapidly progressive. It is for this group of patients with severe autoimmune disease that alternative therapies have been sought, including HCT. The primary concept underlying the use of HCT for these diseases is this: ablating and "resetting" the immune system can alter the disease process by inducing a sustained remission that possibly leads to cure.[1]

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are considered antigenically "naive" and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome with allogenic HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

AUTOLOGOUS HCT

The goal of autologous HCT in patients with autoimmune diseases is to eliminate self-reactive lymphocytes (lymphoablation) and generate new, self-tolerant lymphocytes.[2] This approach is in contrast to destroying the entire hematopoietic bone marrow (myeloablation), as is often performed in autologous HCT for hematologic malignancies.[2] Both lymphoablative and myeloablative regimens are used in patients with an autoimmune disease; however, there is no standard conditioning regimen.[1] The efficacy of the different conditioning regimens has not been compared in clinical trials.[1]

Currently, for autoimmune diseases, autologous transplant is preferred over allogeneic, in part because of the lower toxicity of autotransplant relative to allogeneic, the graft-versus-host disease associated with allogeneic transplant, and the need to administer posttransplant immunosuppression after an allogeneic transplant.[1]

ALLOGENEIC HCT

Experience of using allogeneic HCT for autoimmune diseases is currently limited,[1] but has two potential advantages over autologous transplant. First, the use of donor cells from a genetically different individual could possibly eliminate genetic susceptibility to the autoimmune disease and potentially result in a cure. Second, there exists a possible graft-versus-autoimmune effect, in which the donor T cells attack the transplant recipient's autoreactive immune cells.[1]

REGULATORY STATUS

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

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

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

REFERENCES

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

1. Nikolov NP, Pavletic SZ. Technology Insight: hematopoietic stem cell transplantation for systemic rheumatic disease. Nat Clin Pract Rheumatol. Apr 2008;4(4):184-191. PMID 18285764
2. 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. Dec 2006;54(12):3750-3760. PMID 17133541
3. Milanetti F, Abinun M, Voltarelli JC, et al. Autologous hematopoietic stem cell transplantation for childhood autoimmune disease. Pediatr Clin North Am. Feb 2010;57(1):239-271. PMID 20307720
4. Sullivan KM, Muraro P, Tyndall A. Hematopoietic cell transplantation for autoimmune disease: updates from Europe and the United States. Biol Blood Marrow Transplant. Jan 2010;16(1 Suppl):S48-56. PMID 19895895
5. Mancardi GL, Sormani MP, Gualandi F, et al. Autologous hematopoietic stem cell transplantation in multiple sclerosis: a phase II trial. Neurology. Mar 10 2015;84(10):981-988. PMID 25672923
6. Reston JT, Uhl S, Treadwell JR, et al. Autologous hematopoietic cell transplantation for multiple sclerosis: a systematic review. Mult Scler. Feb 2011;17(2):204-213. PMID 20921236
7. Shevchenko JL, Kuznetsov AN, Ionova TI, et al. Autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis. Exp Hematol. Nov 2012;40(11):892-898. PMID 22771495
8. Shevchenko JL, Kuznetsov AN, Ionova TI, et al. Long-term outcomes of autologous hematopoietic stem cell transplantation with reduced-intensity conditioning in multiple sclerosis: physician's and patient's perspectives. Ann Hematol. Jul 2015;94(7):1149-1157. PMID 25711670

9. 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. Jun 2012;18(6):835-842. PMID 22127896
10. Burt RK, Balabanov R, Han X, et al. Association of nonmyeloablative hematopoietic stem cell transplantation with neurological disability in patients with relapsing-remitting multiple sclerosis. JAMA. Jan 20 2015; 313(3):275-284. PMID 25602998
11. Fassas A, Kimiskidis VK, Sakellari I, et al. Long-term results of stem cell transplantation for MS: a single-center experience. Neurology. Mar 22 2011;76(12):1066-1070. PMID 21422458
12. Burman J, Iacobaeus E, Svenningsson A, et al. Autologous haematopoietic stem cell transplantation for aggressive multiple sclerosis: the Swedish experience. J Neurol Neurosurg Psychiatry. Oct 2014;85(10):1116-1121. PMID 24554104
13. Atkins HL, Bowman M, Allan D, et al. Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial. Lancet. Aug 06 2016; 388(10044):576-585. PMID 27291994
14. 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
15. 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
16. 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
17. 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
18. 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, randomised phase 2 trial. Lancet. Aug 06 2011;378(9790):498-506. PMID 21777972
19. 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. Jan 2008;67(1):98-104. PMID 17526554
20. Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med. Jan 2005;118(1):2-10. PMID 15639201
21. 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. Aug 15 2007;110(4):1388-1396. PMID 17452515
22. 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. Feb 2012;39(2):269-275. PMID 22247352
23. Burt RK, Traynor A, Statkute L, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. JAMA. Feb 01 2006;295(5):527-535. PMID 16449618
24. Song XN, Lv HY, Sun LX, et al. Autologous stem cell transplantation for systemic lupus erythematosus: report of efficacy and safety at 7 years of follow-up in 17 patients. Transplant Proc. Jun 2011;43(5):1924-1927. PMID 21693301
25. Leng XM, Jiang Y, Zhou DB, et al. Good outcome of severe lupus patients with high-dose immunosuppressive therapy and autologous peripheral blood stem cell transplantation: a 10-year follow-up study. Clin Exp Rheumatol. May-Jun 2017;35(3):494-499. PMID 28240594
26. Saccardi R, DiGioia M, Bosi A. Haematopoietic stem cell transplantation for autoimmune disorders. Curr Opin Hematol. Nov 2008;15(6):594-600. PMID 18832930
27. Kazmi MA, Mahdi-Rogers M, Sanvito L. Chronic inflammatory demyelinating polyradiculoneuropathy: a role for haematopoietic stem cell transplantation? Autoimmunity. Dec 2008;41(8):611-615. PMID 18958756

28. Lehmann HC, Hughes RA, Hartung HP. Treatment of chronic inflammatory demyelinating polyradiculoneuropathy. Handb Clin Neurol. Aug 2013;115:415-427. PMID 23931793
29. Peltier AC, Donofrio PD. Chronic inflammatory demyelinating polyradiculoneuropathy: from bench to bedside. Semin Neurol. Jul 2012;32(3):187-195. PMID 23117943
30. El-Badawy A, El-Badri N. Clinical efficacy of stem cell therapy for diabetes mellitus: a meta-analysis. PLoS One. 2016;11(4):e0151938. PMID 27073927
31. Cantu-Rodriguez OG, Lavalle-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
32. 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
33. Snarski E, Milczarczyk A, Halaburda K, et al. Immunoablation and autologous hematopoietic stem cell transplantation in the treatment of new-onset type 1 diabetes mellitus: long-term observations. Bone Marrow Transplant. Mar 2016;51(3):398-402. PMID 26642342
34. 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. Apr 15 2009;301(15):1573-1579. PMID 19366777
35. Bryant A, Atkins H, Pringle CE, et al. Myasthenia gravis treated with autologous hematopoietic stem cell transplantation. JAMA Neurol. Jun 01 2016;73(6):652-658. PMID 27043206
36. 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
37. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Nov 2015;21(11):1863-1869. PMID 26256941
38. Snowden JA, Saccardi R, Allez M, et al. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. Jun 2012; 47(6):770-790. PMID 22002489
39. 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
40. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) (110.23). 2016; https://www.cms.gov/medicare-coveragedatabase/details/ncddetails.aspx?NCDId=366&ncdver=1&DocID=110.23&FriendlyError=NoNCDIDVersion&bc=gAAAABAAAAAAAA%3d%3d&. Accessed December 1, 2017.