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FEP Medical Policy Manual

FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Effective Policy Date: **April 1, 2020**

Original Policy Date: **December 2011**

Related Policies:

2.01.26 - Prolotherapy
7.01.48 - Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Description

Mesenchymal stem cells (MSCs) have the capability to differentiate into a variety of tissue types, including various musculoskeletal tissues. Potential uses of MSCs for orthopedic applications include treatment of damaged bone, cartilage, ligaments, tendons, and intervertebral discs.

OBJECTIVE

The objective of this evidence review is to evaluate whether the use of mesenchymal stem cells in conjunction with interventions for orthopedic conditions improves the net health outcome.

POLICY STATEMENT

Mesenchymal stem cell therapy is considered **investigational** for all orthopedic applications, including use in repair or regeneration of musculoskeletal tissue.

Allograft bone products containing viable stem cells, including but not limited to demineralized bone matrix with stem cells, are considered **investigational** for all orthopedic applications.

Allograft or synthetic bone graft substitutes that must be combined with autologous blood or bone marrow are considered **investigational** for all orthopedic applications.

POLICY GUIDELINES

This policy does not address unprocessed allograft bone.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

The Regenexx procedure is currently performed at select centers in the United States.

FDA REGULATORY STATUS

The 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, Title 21, parts 1270 and 1271. MSCs are included in these regulations.

The regulatory status of the stem cell or stem cell-containing products addressed in this review is summarized below.

Concentrated autologous MSCs do not require approval by the FDA. No products using engineered or expanded MSCs have been approved by the FDA for orthopedic applications.

The following products are examples of commercialized demineralized bone matrix (DBM) products. They are marketed as containing viable stem cells. In some instances, manufacturers have received communications and inquiries from the FDA related to the appropriateness of their marketing products that are dependent on living cells for their function. The following descriptions are from the product literature.

- AlloStem (AlloSource) is a partially demineralized allograft bone seeded with adipose-derived MSCs.
- Map3 (RTI Surgical) contains cortical cancellous bone chips, DBM, and cryopreserved multipotent adult progenitor cells (MAPC).
- Osteocel Plus (NuVasive) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Trinity Evolution Matrix™ (Orthofix) is a DBM combined with viable MSCs isolated from allogeneic bone marrow.
- Other products contain DBM alone and are designed to be mixed with bone marrow aspirate:
    - Fusion Flex™ (Wright Medical) is a dehydrated moldable DBM scaffold (strips and cubes) that will absorb autologous bone marrow aspirate;
    - Ignite (Wright Medical) is an injectable graft with DBM that can be combined with autologous bone marrow aspirate.

A number of DBM combination products have been cleared for marketing by the FDA through the 510(k) process. FDA product code: MQV.

Table 1 provides a representative sample of these products; some of which are specifically labeled for mixing with bone marrow aspirate.

Table 1. Demineralized Bone Matrix Products Cleared by FDA

Product	Matrix Type	Mix With Autologous MSCs	Manufacturer or Sponsor	Date Cleared	510(k) No.
Vitoss Bioactive Foam Bone Graft Substitute	Type I bovine collagen	X	Stryker	Nov 2008	K083033
NanOss BVF-E	Nanocrystalline hydroxyapatite		Pioneer Surgical	Aug 2008	
OrthoBlast II Demineralized bone matrix putty and paste	Human cancellous bone chips		SeaSpine	Sep 2007	K070751
CopiOs Bone Void Filler (sponge and powder disc)	Type I bovine dermal collagen	X	Kensey Nash	May 2007	K071237
DBX Demineralized bone matrix putty, paste and mix	Processed human bone and sodium hyaluronate	X	Musculoskeletal Transplant Foundation	Dec 2006	K053218
Integra MOZAIK™ Osteoconductive Scaffold-Putty	Human cancellous bone	X	IsoTis OrthoBiologics	Dec 2006	K062353
Formagraft™ Collagen Bone Graft Matrix	Bovine fibrillary collagen	X	R and L Medical	May 2005	K050789
DynaGraft II Gel and Putty	Processed human bone particles		IsoTis Orthobiologics	Mar 2005	K040419

FDA: Food and Drug Administration; MSCs: mesenchymal stem cells.

In 2017, the FDA published "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use" https://www.fda.gov/media/124138/download

Human cells, tissues, and cellular and tissue-based products (HCT/P) are defined as human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. If an HCT/P does not meet the criteria below and does not

qualify for any of the stated exceptions, the HCT/P will be regulated as a drug, device, and/or biological product and applicable regulations and premarket review will be required.

An HCT/P is regulated solely under section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria:

"1) The HCT/P is minimally manipulated;

2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer"s objective intent;

3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

4) Either: i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or

ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: a) Is for autologous use; b) Is for allogeneic use in a first-degree or second-degree blood relative; or c) Is for reproductive use."

The FDA does not consider the use of stem cells for orthopedic procedures to be homologous use. In June 2019, the FDA issued a statement on a stem cell clinic permanent injunction and FDA's ongoing efforts to protect patients from risks of unapproved stem cell products.[2,]

RATIONALE

Summary of Evidence

For individuals who have cartilage defects, meniscal defects, joint fusion procedures, or osteonecrosis who receive stem cell therapy, the evidence includes small randomized controlled trials (RCTs) and nonrandomized comparative trials. The relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Use of mesenchymal stem cells (MSCs) for orthopedic conditions is an active area of research. Despite continued research into the methods of harvesting and delivering treatment, there are uncertainties regarding the optimal source of cells and the delivery method. Studies have included MSCs from bone marrow, adipose tissue, and peripheral blood. Overall, the quality of evidence is low and there is a possibility of publication bias. The strongest evidence to date is on MSCs expanded from bone marrow, which includes several phase 1/2 RCTs. Limitations in these initial trials preclude reaching conclusions, but the results to date do support future study in phase 3 trials. Alternative methods of obtaining MSCs have been reported in a smaller number of trials and with mixed results. Additional study in a larger sample of patients with longer follow-up would be needed to evaluate the long-term efficacy and safety of these procedures. Also, expanded MSCs for orthopedic applications are not FDA approved (concentrated autologous MSCs do not require agency approval). Overall, there is a lack of evidence that clinical outcomes are improved. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Association of Orthopaedic Surgeons

The 2013 and 2014 American Association of Orthopaedic Surgeons" guidelines on the treatment of glenohumeral joint osteoarthritis have indicated that:

- Treatment using an allograft, autograft, biologic, and interpositional grafts in patients with glenohumeral joint osteoarthritis is inconclusive[24]; and that
- Treatment using growth factor injections and/or platelet-rich plasma for patients with symptomatic osteoarthritis of the knee is inconclusive.[25]

American Association of Neurological Surgeons

The American Association of Neurological Surgeons (2014) guidelines on fusion procedures for degenerative disease of the lumbar spine relevant to this evidence review have indicated that "The use of demineralized bone matrix (DBM) as a bone graft extender is an option for 1- and 2-level instrumented posterolateral fusions. Demineralized Bone Matrix: Grade C (poor level of evidence)."[26]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

REFERENCES

1. Goldberg A, Mitchell K, Soans J, et al. The use of mesenchymal stem cells for cartilage repair and regeneration: a systematic review. Mar 09 2017;12(1):39. PMID 28279182
2. U.S. Food and Drug Administration. Letter from Mary A. Malarkey, Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research to Christopher J. Centeno, M.D., Medical Director, Regenerative Sciences, Inc. 2008 Jul 25; https://wayback.archive-it.org/7993/20170112214943/http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/ucm091991.htm. Accessed December 30, 2019.
3. Borakati A, Mafi R, Mafi P, et al. A systematic review and meta-analysis of clinical trials of mesenchymal stem cell therapy for cartilage repair. Curr Stem Cell Res Ther. Sep 15 2017. PMID 28914207
4. Wakitani S, Imoto K, Yamamoto T, et al. Human autologous culture expanded bone marrow mesenchymal cell transplantation for repair of cartilage defects in osteoarthritic knees. Osteoarthritis Cartilage. Mar 2002;10(3):199-206. PMID 11869080
5. Wakitani S, Nawata M, Tensho K, et al. Repair of articular cartilage defects in the patello-femoral joint with autologous bone marrow mesenchymal cell transplantation: three case reports involving nine defects in five knees. J Tissue Eng Regen Med. Jan-Feb 2007;1(1):74-79. PMID 18038395
6. Wakitani S, Okabe T, Horibe S, et al. Safety of autologous bone marrow-derived mesenchymal stem cell transplantation for cartilage repair in 41 patients with 45 joints followed for up to 11 years and 5 months. J Tissue Eng Regen Med. Feb 2011;5(2):146-150. PMID 20603892
7. Centeno CJ, Schultz JR, Cheever M, et al. Safety and complications reporting on the re-implantation of culture-expanded mesenchymal stem cells using autologous platelet lysate technique. Curr Stem Cell Res Ther. Dec 2 2010;5(1):81-93. PMID 19951252
8. Wong KL, Lee KB, Tai BC, et al. Injectable cultured bone marrow-derived mesenchymal stem cells in varus knees with cartilage defects undergoing high tibial osteotomy: a prospective, randomized controlled clinical trial with 2 years' follow-up. Arthroscopy. Dec 2013;29(12):2020-2028. PMID 24286801
9. Emadedin M, Labibzadeh N, Liastani MG, et al. Intra-articular implantation of autologous bone marrow-derived mesenchymal stromal cells to treat knee osteoarthritis: a randomized, triple-blind, placebo-controlled phase 1/2 clinical trial. Cytotherapy. 2018

Oct;20(10):1238-1246. PMID 30318332
10. Lamo-Espinosa JM, Mora G, Blanco JF, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: long-term follow-up of a multicenter randomized controlled clinical trial (phase I/II). J Transl Med. 2018 Jul;16(1). PMID 30064455
11. Lamo-Espinosa JM, Mora G, Blanco JF et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II). J Transl Med. 2016 Aug;14(1). PMID 27565858
12. Vega A, Martin-Ferrero MA, Del Canto F, et al. Treatment of knee osteoarthritis with allogeneic bone marrow mesenchymal stem cells: a randomized controlled trial. Transplantation. Aug 2015;99(8):1681-1690. PMID 25822648
13. Shapiro SA, Kazmerchak SE, Heckman MG, et al. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. Am J Sports Med. Jan 2017;45(1):82-90. PMID 27566242
14. Koh YG, Kwon OR, Kim YS, et al. Comparative outcomes of open-wedge high tibial osteotomy with platelet-rich plasma alone or in combination with mesenchymal stem cell treatment: a prospective study. Arthroscopy. Nov 2014;30(11):1453-1460. PMID 25108907
15. Saw KY, Anz A, Siew-Yoke Jee C, et al. Articular cartilage regeneration with autologous peripheral blood stem cells versus hyaluronic acid: a randomized controlled trial. Arthroscopy. Apr 2013;29(4):684-694. PMID 23380230
16. Whitehouse MR, Howells NR, Parry MC, et al. Repair of torn avascular meniscal cartilage using undifferentiated autologous mesenchymal stem cells: from in vitro optimization to a first-in-human study. Stem Cells Transl Med. Apr 2017;6(4):1237-1248. PMID 28186682
17. Vangsness CT, Jr., Farr J, 2nd, Boyd J, et al. Adult human mesenchymal stem cells delivered via intra-articular injection to the knee following partial medial meniscectomy: a randomized, double-blind, controlled study. J Bone Joint Surg Am. Jan 15 2014;96(2):90-98. PMID 24430407
18. Vanichkachorn J, Peppers T, Bullard D, et al. A prospective clinical and radiographic 12-month outcome study of patients undergoing single-level anterior cervical discectomy and fusion for symptomatic cervical degenerative disc disease utilizing a novel viable allogeneic, cancellous, bone matrix (trinity evolution) with a comparison to historical controls. Eur Spine J. Jul 2016;25(7):2233-2238. PMID 26849141
19. Peppers TA, Bullard DE, Vanichkachorn JS, et al. Prospective clinical and radiographic evaluation of an allogeneic bone matrix containing stem cells (Trinity Evolution(R) Viable Cellular Bone Matrix) in patients undergoing two-level anterior cervical discectomy and fusion. J Orthop Surg Res. Apr 26 2017;12(1):67. PMID 28446192
20. Jones CP, Loveland J, Atkinson BL, et al. Prospective, multicenter evaluation of allogeneic bone matrix containing viable osteogenic cells in foot and/or ankle arthrodesis. Foot Ankle Int. Oct 2015;36(10):1129-1137. PMID 25976919
21. Eastlack RK, Garfin SR, Brown CR, et al. Osteocel plus cellular allograft in anterior cervical discectomy and fusion: evaluation of clinical and radiographic outcomes from a prospective multicenter study. Spine (Phila Pa 1976). Oct 15 2014;39(22):E1331-1337. PMID 25188591
22. Sen RK, Tripathy SK, Aggarwal S, et al. Early results of core decompression and autologous bone marrow mononuclear cells instillation in femoral head osteonecrosis: a randomized control study. J Arthroplasty. May 2012;27(5):679-686. PMID 22000577
23. Zhao D, Cui D, Wang B, et al. Treatment of early stage osteonecrosis of the femoral head with autologous implantation of bone marrow-derived and cultured mesenchymal stem cells. Bone. Jan 2012;50(1):325-330. PMID 22094904
24. American Academy of Orthopaedic Surgeons (AAOS). American Academy of Orthopaedic Surgeons clinical practice guideline on the treatment of glenohumeral joint osteoarthritis. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2009 (affirmed 2014).
25. American Academy of Orthopaedic Surgeons (AAOS). American Academy of Orthopaedic Surgeons clinical practice guideline on treatment of osteoarthritis of the knee. 2nd ed. Rosemont, IL: American Academy of Orthopaedic Surgeons; 2013.
26. Kaiser MG, Groff MW, Watters WC, 3rd, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes as an adjunct for lumbar fusion. J Neurosurg Spine. Jul 2014;21(1):106-132. PMID 24980593

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
September 2012	Replace policy	Updated literature search, reference number 6 added; remaining references renumbered.

Date	Action	Description
September 2013	Replace policy	Policy updated with literature review. References 4, 7, 11-16 and 18 added, renumbered and removed; addition of policy statement that allograft bone containing viable stem cells is considered investigational.
June 2014	Replace policy	Policy updated with literature review; references 5, 13, and 17 added; policy statements unchanged.
October 2015	Replace policy	Policy updated with literature review; references 3, 14, 16, 18, 20, and 22 added. Investigational statement added on bone graft substitutes that must be used with autologous blood or bone marrow aspirate. Policy title change: “Orthopedic applications of stem cell therapy (including allograft and bone substitute products used with autologous bone marrow)”.
March 2018	Replace policy	Policy updated with literature review through November 29, 2017; references 1, 2, 4, 12-15, 24-25 and 27-29 added/updated. Policy statements unchanged. Title changed to “Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow).”
March 2019	Replace policy	Policy updated with literature review through November 29, 2017; references 14 and 24 added; references 2 and 4 updated. Policy statements unchanged.
March 2020	Replace policy	Policy updated with literature review through November 19, 2019; references added. Policy statements unchanged.