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FEP Medical Policy Manual

FEP 8.01.52 Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

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Original Policy Date: December 2011

Related Policies:

2.01.26 - Prolotherapy
2.01.98 - Orthopedic Applications of Platelet-Rich Plasma
7.01.48 - Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Description

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 or products that do not require mixing with stem cells (product examples are shown in Tables 1 and 2 for informational purposes).

BENEFIT APPLICATION

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

Stem cell injections are currently performed at select centers in the United States. Therefore, requests for it may be made for an out-of-network facility.

FDA REGULATORY STATUS

The U.S. Food and Drug Administration (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.

Tables 1 and 2 provide a representative sample of these products, differentiated by whether they must be mixed with autologous MSCs.

Table 1. Examples of Demineralized Bone Matrix Products Cleared by FDA that Do Not Require Mixing with Autologous MSCs

Product	Matrix Type		Manufacturer or Sponsor	Date Cleared	510(k) No.
Vitoss Bioactive Foam Bone Graft Substitute	Type I bovine collagen		Stryker	Nov 2008	K083033
NanOss BVF-E	Nanocrystalline hydroxyapatite		Pioneer Surgical	Aug 2008	K081558
OrthoBlast II Demineralized bone matrix putty and paste	Human (mixed allograft donor-derived) cancellous bone chips		SeaSpine	Sep 2007	K070751
DBX Demineralized bone matrix putty, paste and mix	Processed human (single allograft donor-derived) bone and sodium hyaluronate		Musculoskeletal Transplant Foundation	Dec 2006	K053218
Formagraft™ Collagen Bone Graft Matrix	Bovine fibrillary collagen		R and L Medical	May 2005	K050789
DynaGraft II Gel and Putty	Processed human (mixed allograft donor-derived) bone particles		IsoTis Orthobiologics	Mar 2005	K040419

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

Table 2. Examples of Demineralized Bone Matrix Products Cleared by FDA that Require Mixing with Autologous MSCs

Product	Matrix Type	Manufacturer or Sponsor	Date Cleared	510(k) No.
CopiOs Bone Void Filler (sponge and powder disc)	Type I bovine dermal collagen	Kensey Nash	May 2007	K071237
Integra MOZAIK™ Osteoconductive Scaffold-Putty	Collagen matrix with tricalcium phosphate granules	IsoTis OrthoBiologics	Dec 2006	K062353

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

In 2020, the FDA updated their guidance on "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use.[2,]

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.

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 randomized controlled trials (RCTs) and nonrandomized comparative trials. 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 autologous MSCs expanded from bone marrow, which includes several phase 1/2 RCTs and a phase 3 RCT (which also evaluated other cell therapies). The phase 3 trial did not indicate significant improvements with the cell therapy modalities relative to active-control intra-articular corticosteroid injections for patients with knee osteoarthritis after 12 months of follow-up. Another recent phase 3 RCT evaluated autologous MSCs expanded from abdominal adipose tissue for treatment of knee osteoarthritis; this trial indicated autologous adipose-derived MSCs were more effective than matching placebo injections in improving pain, function, and other patient-reported outcomes after 6 months of follow-up. These phase 3 trials' mixed findings may be related to differences in the cell therapy modalities used, baseline cohort characteristics, and/or the use of an active vs placebo control. Alternative methods of obtaining MSCs have been reported in a smaller number of trials and with mixed results. Additional study with longer follow-up is needed to evaluate the long-term efficacy and safety of these procedures. Also, expanded MSCs for orthopedic applications are not U.S. Food and Drug Administration approved (concentrated autologous MSCs do not require agency approval). Overall, there is a lack of clear evidence that clinical outcomes are improved. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Orthopaedic Surgeons

A 2020 guideline from American Association of Orthopaedic Surgeons on the management of glenohumeral joint osteoarthritis (OA) , endorsed by several other societies, states that injectable biologics such as stem cells cannot be recommended in the treatment glenohumeral joint OA.[31,] There was consensus from the panel that better standardization and high-quality evidence from clinical trials is needed to provide definitive evidence on the efficacy of biologics in glenohumeral OA. The strength of evidence was rated as no reliable scientific evidence to determine benefits and harms.

The 2021 guideline on treatment of osteoarthritis of the knee does not address stem cell injections.[32,]

American Association of Neurological Surgeons

In 2014, the American Association of Neurological Surgeons 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)."[33,]

American College of Rheumatology and Arthritis Foundation

In 2019, guidelines from the American College of Rheumatology and Arthritis Foundation on OA of the hand, hip, and knee gave a strong recommendation against stem cell injections in patients with knee and/or hip OA, noting the heterogeneity in preparations and lack of standardization of techniques.[34,] No recommendation was made for hand OA, since efficacy of stem cells has not been evaluated.

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. J Orthop Surg Res. Mar 09 2017; 12(1): 39. PMID 28279182
2. U.S. Food & Drug Administration. Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal. Accessed November 10, 2023.
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. Feb 23 2018; 13(3): 215-225. PMID 28914207
4. Maheshwer B, Polce EM, Paul K, et al. Regenerative Potential of Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis and Chondral Defects: A Systematic Review and Meta-analysis. Arthroscopy. Jan 2021; 37(1): 362-378. PMID 32497658
5. Wiggers TG, Winters M, Van den Boom NA, et al. Autologous stem cell therapy in knee osteoarthritis: a systematic review of randomised controlled trials. Br J Sports Med. Oct 2021; 55(20): 1161-1169. PMID 34039582

6. Kim SH, Djaja YP, Park YB, et al. Intra-articular Injection of Culture-Expanded Mesenchymal Stem Cells Without Adjuvant Surgery in Knee Osteoarthritis: A Systematic Review and Meta-analysis. Am J Sports Med. Sep 2020; 48(11): 2839-2849. PMID 31874044
7. Jin L, Yang G, Men X, et al. Intra-articular Injection of Mesenchymal Stem Cells After High Tibial Osteotomy: A Systematic Review and Meta-analysis. Orthop J Sports Med. Nov 2022; 10(11): 23259671221133784. PMID 36452339
8. 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
9. 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. 2007; 1(1): 74-9. PMID 18038395
10. 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): 146-50. PMID 20603892
11. 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. Mar 2010; 5(1): 81-93. PMID 19951252
12. 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): 2020-8. PMID 24286801
13. 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. Oct 2018; 20(10): 1238-1246. PMID 30318332
14. 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. Jul 31 2018; 16(1): 213. PMID 30064455
15. 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. Aug 26 2016; 14(1): 246. PMID 27565858
16. Mautner K, Gottschalk M, Boden SD, et al. Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial. Nat Med. Nov 02 2023. PMID 37919438
17. Vega A, Martn-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): 1681-90. PMID 25822648
18. 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
19. 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): 1453-60. PMID 25108907
20. Zaffagnini S, Andriolo L, Boffa A, et al. Microfragmented Adipose Tissue Versus Platelet-Rich Plasma for the Treatment of Knee Osteoarthritis: A Prospective Randomized Controlled Trial at 2-Year Follow-up. Am J Sports Med. Sep 2022; 50(11): 2881-2892. PMID 35984721
21. Kim KI, Lee MC, Lee JH, et al. Clinical Efficacy and Safety of the Intra-articular Injection of Autologous Adipose-Derived Mesenchymal Stem Cells for Knee Osteoarthritis: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial. Am J Sports Med. Jul 2023; 51(9): 2243-2253. PMID 37345256
22. Lim HC, Park YB, Ha CW, et al. Allogeneic Umbilical Cord Blood-Derived Mesenchymal Stem Cell Implantation Versus Microfracture for Large, Full-Thickness Cartilage Defects in Older Patients: A Multicenter Randomized Clinical Trial and Extended 5-Year Clinical Follow-up. Orthop J Sports Med. Jan 2021; 9(1): 2325967120973052. PMID 33490296
23. 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
24. Vangsness CT, Farr J, 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): 90-8. PMID 24430407
25. 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): 2233-8. PMID 26849141
26. Peppers TA, Bullard DE, Vanichkachorn JS, et al. Prospective clinical and radiographic evaluation of an allogeneic bone matrix containing stem cells (Trinity Evolution 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
27. 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): 1129-37. PMID 25976919
28. 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): E1331-7. PMID 25188591
29. 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): 679-86. PMID 22000577
30. 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): 325-30. PMID 22094904
31. American Academy of Orthopaedic Surgeons. Management of Glenohumeral Joint Osteoarthritis Evidence-Based Clinical Practice Guideline. https://www.aaos.org/globalassets/quality-and-practice-resources/glenohumeral/gjo-cpg.pdf. Updated March 23, 2020. Accessed November 10, 2023.

32. American Academy of Orthopaedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty). https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf. Updated August 31, 2021. Accessed November 9, 2023.
33. Kaiser MG, Groff MW, Watters WC, 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): 106-32. PMID 24980593
34. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Care Res (Hoboken). Feb 2020; 72(2): 149-162. PMID 31908149

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.
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.
March 2021	Replace policy	Policy updated with literature review through December 4, 2020; references added. Policy statements unchanged.
March 2022	Replace policy	Policy updated with literature review through December 17, 2021; references added. Policy statements unchanged.
March 2023	Replace policy	Policy updated with literature review through December 5, 2022; references added. Policy statements unchanged.
March 2024	Replace policy	Policy updated with literature review through November 10, 2023; references added. Policy statements unchanged. Language added to policy guidelines to clarify that bone matrix products that do not involve stem cell use are not evaluated in this review.