Protocol

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

(70148)

Medical Benefit		**Effective Date**: 04/01/18	**Next Review Date**: 01/21
Preauthorization	Yes	**Review Dates**: 02/07, 02/08, 03/09, 01/10, 01/11, 09/11, 09/12, 09/13, 07/14, 07/15, 01/16, 01/17, 01/18, 01/19, 01/20	

Preauthorization is required.

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 focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyle, trochlea, or patella	Interventions of interest are: • Autologous chondrocyte implantation	Comparators of interest are: • Marrow stimulation • Osteochondral autografts	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life
Individuals: • With focal articular cartilage lesions of joints other than the knee	Interventions of interest are: • Autologous chondrocyte implantation	Comparators of interest are: • Marrow stimulation • Osteochondral autografts	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Quality of life

DESCRIPTION

A variety of procedures are being developed to resurface articular cartilage defects. Autologous chondrocyte implantation (ACI) involves harvesting chondrocytes from healthy tissue, expanding the cells in vitro, and implanting the expanded cells into the chondral defect. Second- and third-generation techniques include combinations of autologous chondrocytes, scaffolds, and growth factors.

SUMMARY OF EVIDENCE

For individuals who have focal articular cartilage lesion(s) of the weight-bearing surface of the femoral condyles, trochlea, or patella who receive ACI, the evidence includes systematic reviews, randomized controlled trials, and prospective observational studies. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. There is a large body of evidence on ACI for the treatment of focal articular cartilage lesions of the knee. For large lesions, ACI results in better outcomes than microfracture, particularly in the long-term. In addition, there is a limit to the size of lesions that can be treated with osteochondral autograft transfer, due to a limit on the number of osteochondral cores that can be safely harvested. As a result, ACI has become the established treatment for large articular cartilage lesions in the knee. In 2017, first-genera-

tion ACI with a collagen cover was phased out and replaced with an ACI preparation that seeds the chondrocytes onto a bioresorbable collagen sponge. Although the implantation procedure for this second-generation ACI is less technically demanding, studies to date have not shown improved outcomes compared with first-generation ACI. Some evidence has suggested an increase in hypertrophy (overgrowth) of the new implant that may exceed that of the collagen membrane covered implant. Long-term studies with a larger number of patients will be needed to determine whether this hypertrophy impacts graft survival. Based on mid-term outcomes that approximate those of first-generation ACI and the lack of alternatives, second-generation ACI may be considered an option for large disabling full-thickness cartilage lesions of the knee. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have focal articular cartilage lesions of joints other than the knee who receive ACI, the evidence includes systematic reviews of case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, and quality of life. The greatest amount of literature is for ACI of the talus. Comparative trials are needed to determine whether ACI improves outcomes for lesions in joints other than the knee. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input has been requested on multiple occasions, obtained most recently in 2015, on the use of ACI in the patella. Prior input supported use for localized chondral defects when other treatments have not been successful. The most recent input was generally supportive of the use of ACI for large patellar lesions, although the degree of support varied. Reviewers indicated that outcomes were improved when realignment procedures are performed concurrently with ACI of the patella and that success rates are lower when using ACI after a prior microfracture. Most reviewers recommended that a prior surgical procedure not be required for lesions greater than four cm^2.

POLICY

Autologous chondrocyte implantation may be considered **medically necessary** for the treatment of disabling full thickness articular cartilage defects of the knee caused by acute or repetitive trauma when all of the following criteria are met:

- Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years).
- Focal, full thickness (grade III or IV) unipolar lesions of the weight-bearing surface of the femoral condyles, trochlea, or patella at least 1.5 cm^2 in size
- Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge Grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect
- Normal knee biomechanics or alignment and stability achieved concurrently with autologous chondrocyte implantation.

Autologous chondrocyte implantation for all other joints, including the talar, and any indications other than those listed above is considered **investigational**.

POLICY GUIDELINES

For smaller lesions (e.g., smaller than four cm^2) if debridement is the only prior surgical treatment, then consideration should be given to marrow-stimulating techniques before ACI is performed.

The average defect size reported in the literature is about five cm^2; many studies treated lesions as large as 15 cm^2.

Severe obesity (e.g., body mass index greater than 35 kg/m^2) may affect outcomes due to the increased stress on weight bearing surfaces of the joint.

Misalignment and instability of the joint are contraindications. Therefore, additional procedures, such as repair of ligaments or tendons or creation of an osteotomy for realignment of the joint, may be performed at the same time. In addition, meniscal allograft transplantation may be performed in combination, either concurrently or sequentially, with ACI.

The entire matrix-induced ACI procedure consists of four steps: 1) initial arthroscopy and biopsy of normal cartilage, 2) culturing of chondrocytes on an absorbable collagen matrix, 3) a separate arthrotomy to place the implant, and 4) postsurgical rehabilitation. The initial arthroscopy may be scheduled as a diagnostic procedure; as part of this procedure, a cartilage defect may be identified, prompting biopsy of normal cartilage in anticipation of a possible chondrocyte transplant. The biopsied material is then sent for culturing and returned to the hospital when the implantation procedure (i.e., arthrotomy) is scheduled.

BACKGROUND

ARTICULAR CARTILAGE LESIONS

Damaged articular cartilage typically fails to heal on its own and can be associated with pain, loss of function, and disability, and may lead to debilitating osteoarthritis over time. These manifestations can severely impair a patient's activities of daily living and adversely affect quality of life.

Treatment

Conventional treatment options include débridement, subchondral drilling, microfracture, and abrasion arthroplasty. Débridement involves the removal of synovial membrane, osteophytes, loose articular debris, diseased cartilage, and is capable of producing symptomatic relief. Subchondral drilling, microfracture, and abrasion arthroplasty attempt to restore the articular surface by inducing the growth of fibrocartilage into the chondral defect. Compared with the original hyaline cartilage, fibrocartilage has less capability to withstand shock or shearing force and can degenerate over time, often resulting in the return of clinical symptoms. Osteochondral grafts and autologous chondrocyte implantation (ACI) attempt to regenerate hyaline-like cartilage and thereby restore durable function. Osteochondral grafts for the treatment of articular cartilage defects are discussed in the Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions Protocol.

With ACI, a region of healthy articular cartilage is identified and biopsied through arthroscopy. The tissue is sent to a facility licensed by the U.S. Food and Drug Administration (FDA) where it is minced and enzymatically digested, and the chondrocytes are separated by filtration. The isolated chondrocytes are cultured for 11 to 21 days to expand the cell population, tested, and then shipped back for implantation. With the patient under general anesthesia, an arthrotomy is performed, and the chondral lesion is excised up to the normal surrounding cartilage. Methods to improve the first-generation ACI procedure have been developed, including the use of a scaffold or matrix-induced autologous chondrocyte implantation (MACI) composed of biocompatible carbohydrates, protein polymers, or synthetics. The only FDA-approved MACI product to date is supplied in a sheet, which is cut to size and fixed with fibrin glue. This procedure is considered technically easier and less time-consuming than the first-generation technique, which required suturing of a periosteal or collagen patch and injection of chondrocytes under the patch.

Desired features of articular cartilage repair procedures are the ability (1) to be implanted easily, (2) to reduce surgical morbidity, (3) not to require harvesting of other tissues, (4) to enhance cell proliferation and matura-

tion, (5) to maintain the phenotype, and (6) to integrate with the surrounding articular tissue. In addition to the potential to improve the formation and distribution of hyaline cartilage, use of a scaffold with MACI eliminates the need for harvesting and suture of a periosteal or collagen patch. A scaffold without cells may also support chondrocyte growth.

REGULATORY STATUS

The culturing of chondrocytes is considered by the FDA to fall into the category of manipulated autologous structural cells, which are subject to a biologic licensing requirement. In 1997, Carticel® (Genzyme; now Vericel) received the FDA approval for the repair of clinically significant, "...symptomatic cartilaginous defects of the femoral condyle (medial lateral or trochlear) caused by acute or repetitive trauma...."

In December 2016, MACI® (Vericel) received the FDA approved for "the repair of symptomatic, single or multiple full-thickness cartilage defects of the knee with or without bone involvement in adults." MACI® consists of autologous chondrocytes that are cultured onto a bioresorbable porcine-derived collagen membrane. In 2017, production of Carticel® was phased out, and MACI® is the only ACI product available in the U.S.

A number of other second-generation methods for implanting autologous chondrocytes in a biodegradable matrix are currently in development or testing or are available outside of the U.S. They include Atelocollagen (Koken), a collagen gel; Bioseed® C (BioTissue Technologies), a polymer scaffold; CaReS (Ars Arthro), collagen gel; Cartilix (Biomet), a polymer hydrogel; Chondron (Sewon Cellontech), a fibrin gel; Hyalograft C (Fidia Advanced Polymers), a hyaluronic acid-based scaffold; NeoCart (Histogenics), an ACI with a three dimensional chondromatrix in a phase three trial; and Novocart®3D (Aesculap Biologics), a collagen-chondroitin sulfate scaffold in a phase three trial. ChondroCelect® (TiGenix), characterized as a chondrocyte implantation with a completed phase three trial, uses a gene marker profile to determine in vivo cartilage-forming potential and thereby optimizes the phenotype (e.g., hyaline cartilage vs. fibrocartilage) of the tissue produced with each ACI cell batch. Each batch of chondrocytes is graded based on the quantitative gene expression of a selection of positive and negative markers for hyaline cartilage formation. Both Hyalograft C and ChondroCelect® have been withdrawn from the market in Europe.

RELATED PROTOCOLS

Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions

Continuous Passive Motion in the Home Setting

Meniscal Allografts and Other Meniscal Implants

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

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

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