NHS England

Clinical Commissioning Policy: Autologous chrondrocyte implantation for osteochondral lesions of the talus

Reference: NHS England: 16012/P

NHS England INFORMATION READER BOX		
Directorate		
Medical	Operations and Information	**Specialised Commissioning**
Nursing	Trans. & Corp. Ops.	Commissioning Strategy
Finance		

Publications Gateway Reference:	**05527s**
Document Purpose	Policy
Document Name	Clinical Commissioning Policy 16012/P
Author	Specialised Commissioning Team
Publication Date	13 July 2016
Target Audience	CCG Clinical Leaders, Care Trust CEs, Foundation Trust CEs , Medical Directors, Directors of PH, Directors of Nursing, NHS England Regional Directors, NHS England Directors of Commissioning Operations, Directors of Finance, NHS Trust CEs
Additional Circulation List	
Description	Not Routinely Commissioned - NHS England will not routinely commission this specialised treatment in accordance with the criteria described in this policy.
Cross Reference	This document is part of a suite of policies with Gateway Reference 05527s.
Superseded Docs (if applicable)	N/A
Action Required	N/A
Timing / Deadlines (if applicable)	**N/A**
Contact Details for further information	england.specialisedcommissioning@nhs.net

Document Status

This is a controlled document. Whilst this document may be printed, the electronic version posted on the intranet is the controlled copy. Any printed copies of this document are not controlled. As a controlled document, this document should not be saved onto local or network drives but should always be accessed from the intranet.

Clinical Commissioning Policy: Autologous chondrocyte implantation for osteochondral lesions of the talus (adults)

First published: July 2016

Prepared by NHS England Specialised Services Clinical Reference Group for Specialised orthopaedic services

Published by NHS England, in electronic format only.

Contents

Policy Statement

NHS England will not routinely commission autologous chondrocyte implantations for osteochondral lesions of the talus in accordance with the criteria outlined in this document. In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources. This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About osteochondral lesions of the talus

A substance called 'cartilage' covers the area where bones meet in the joints. It acts as a cushion and allows the joint to move freely with very little friction. Osteochondral lesions are areas of damage to this cartilage layer.

- This can cause pain, clicking, grinding or instability of the joint.
- If lesions are not treated, this may lead to osteoarthritis and serious disability.

The 'talus' is one of the bones in the ankle joint. It helps to support the weight of the body. Many patients with osteochondral lesions in this area have had previous ankle trauma or injury.

About the current treatment

Patients with osteochondral lesions of the talus are first treated with either:

- 'surgical debridement' – this is where the joint is cleaned out. Other procedures to support the joint or encourage new growth of cartilage may also be done.
- 'bone grafting' – this is where bone tissue from elsewhere in the body is transplanted to the problem area.

About the new treatment

Autologous chondrocyte implantation (ACI) is a procedure that was developed in the late 1980s. It has mainly been used to treat areas of cartilage damage in the knee, but has also been used in other joints including the ankle. The technique requires two operations:

- the first to gather cartilage cells from an undamaged area of the ankle joint – these cells are then 'cultured' in a laboratory to increase their number
- the second to implant these cells into the defect.

The aim is to repair the damaged area by covering the defect with new cartilage. ACI has evolved over many years and a variety of methods have been developed to hold the cells in place on the defect and encourage good quality repair.

What have we decided

NHS England has carefully reviewed the evidence to treat osteochondral lesions of the talus with ACI. We have concluded that there is not enough evidence to make the treatment available at this time.

1 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to not routinely commission ACI for osteochondral lesions of the talus.

Osteochondral lesions (OCLs) are areas of joint damage involving the articular hyaline cartilage and the underlying subchondral bone. These defects can cause pain, clicking, grinding or functional instability of the joint, and may lead to osteoarthritis and serious disability. The defects or lesions are thought to be caused by an ischaemic event affecting the joint (for example as a result of trauma or injury) or spontaneously, a condition called osteochondritis dissecans. Cartilage lacks blood and nerve supplies, and therefore has a limited potential for self-repair.

The ankle joint consists of three bones: the tibia, the fibula and the talus. The talus lies above the calcaneus and supports the weight of the body at the ankle. Osteochondral defects of the talus occur predominantly on the talar dome, which is the uppermost part of the talus. Patients with an osteochondral defect often have unresolved ankle pain.

Patients presenting with symptomatic osteochondral defects are first treated with either surgical debridement (alone or in combination with Kirschner-wire drilling or microfracture of the subchondral bone) or bone grafting. If the first surgery does not resolve the symptoms, patients may be referred to specialist orthopaedic centres for a resurfacing procedure.

Autologous chondrocyte implantation (ACI) is one type of resurfacing procedure, developed in the late 1980s to treat areas of cartilage damage in the knee. However, ACI has also been used rarely in other joints, such as the ankle. Second and third generation approaches have evolved over the years, but ACI is a two-stage procedure. ACI involves harvesting the patient's own chondrocytes from the joint (either healthy articular cartilage taken from a non-articulating area or from the defect itself) during arthroscopic surgery. Chondrocytes are then cultured in a laboratory to increase their number. Chondrocytes can be cultured traditionally or by using

biomarkers to select cells most likely to produce hyaline cartilage; these cells are called characterised chondrocytes. Finally, the chondrocytes are implanted into the area of damaged cartilage during a second surgical procedure, in the hope that they will repair the damaged area. The aim is to repair the damaged area by resurfacing with defect with new hyaline cartilage.

In first generation ACI, the implanted cultured chondrocytes are covered with a cap made from periosteum (ACI-P), fibrous tissue that covers bones. In second generation ACI the cap is made from collagen (ACI-C). The third generation of ACI involved seeding the chondrocytes onto a porcine collagen membrane (ACI-M) to avoid chondrocytes leaking around the cap.

Chondrocelect (Sobi) is currently licensed in the UK for repair of symptomatic cartilage defects of the knee. A number of other commercial ACI products are in clinical trials for knee repair. MACI (Vericel) was approved by the EMA but is no longer available commercially.

2 Definitions

OCLs or osteochondral defects, also known as osteochondritis dissecans, are areas of joint damage involving the articular hyaline cartilage and the underlying subchondral bone. Loss of cartilage alone is referred to as chondral damage.

Osteochondritis dissecans (OCD) is a condition that develops in joints, most often in children and adolescents. It occurs when a small segment of bone begins to separate from its surrounding region due to a lack of blood supply. As a result, the small piece of bone and the cartilage covering it begin to crack and loosen

Arthroscopy is a type of keyhole surgery used both to diagnose and treat joint problems. It is most commonly used on the knees, ankles, shoulders, elbows, wrists and hips.

The talus lies above the calcaneus and supports the weight of the body at the ankle.

Cartilage is a tough, flexible tissue found throughout the body. Articular (hyaline) cartilage, which is composed mainly of water and a collagenous extracellular matrix, provides a smooth and resilient surface at the ends of bones, allowing virtually frictionless movement within the joint. It also acts as a shock absorber.

Chondrocytes are the cellular component of hyaline cartilage, responsible for the production and maintenance of the matrix.

ACI is a biomedical treatment that aims to repair damages in articular cartilage using the patient's own cells.

Matrix-induced autologous chondrocyte implantation (MACI) is a brand of third generation ACI provided in the form of a membrane that has been seeded with chondrocytes.

Microfracture, also known as bone marrow stimulation (BMS), is common procedure aimed at repairing cartilage defects by creating small holes in the surface of the bone and cause bleeding from the underlying bone. Blood from the defect is washed away until a clot forms; this clot is believed to be the optimal environment for tissue to regenerate within the lesion.

Mosaicplasty is a technique of creating an osteochondral autograft by harvesting and transplanting many small cylindrical osteochondral plugs from the less weight-bearing periphery of the joint and inserting them into drilled tunnels in the defective section of cartilage. It is also known as Osteochondral Autograft Transfer System (OATS), a brand of mosaicplasty.

Osteotomy is a surgery that involves adding or removing a small section of bone either above or below the joint.

Bone marrow derived chondrocyte transplantation (BMDCT) is a one-step procedure aimed at repairing cartilage defects by harvesting bone marrow from the patient's iliac crest, concentrating the bone marrow derived cells using a device, and implanting into the osteochondral defect within the same surgery.

3 Aims and Objectives

This policy aims to define NHS England's commissioning position on ACI as part of the treatment pathway for adults with osteochondral lesions of the talus.

The objective is to ensure evidence based commissioning in the use of ACI for the treatment of adults with osteochondral lesions of the talus.

4 Epidemiology and Needs Assessment

OCLs are rare joint disorders. Most often, they affect the knee, followed by the elbow and the talus. Lesions of the talus account for 4% of all osteochondral lesions in the body (Alexander & Lichtman, 1980). In most cases these lesions are thought to be caused by an ischaemic event affecting the joint, however osteochondritis dissecans can also be a cause.

Osteochondritis dissecans is a rare disease, occurring in only 15 to 30 people per 100,000 in the general population each year, most commonly in the knee joint (Obediana and Grelsamera, 1997).

Retrospective analysis has shown that the majority of patients with osteochondral defects have experienced previous ankle trauma, such as a sporting injury. Acutely, osteochondral lesions occur in 6.5% of all ankle sprains. Chronically, they are found in 20.5% of ankle sprains and 57% of cases of ankle disability. OCLs are one of the most important causes of residual pain after ankle sprain. The clinical diagnosis is regarded as difficult, and delay in establishing the diagnosis is common (Davies, 2015).

OCLs of the talus occur frequently in young patients participating in sports activities: the majority occur between the second and fourth decade of life, with the average age being 27 years. It appears that the plane of weakness in this age group lies in the bone rather than at the junction of the cartilage (Giannini et al., 2009). The male-to-female ratio is 2:1.

Approximately 85-90% of patients with OCL of the talus respond to primary surgery, and only 10-15% of patients require further surgery, including a possible resurfacing approach.

5 Evidence Base

NHS England has concluded that there is not sufficient evidence to support a proposal for the routine commissioning of ACI for OCLs of the talus.

Different metrics have been used to assess recovery and clinical effectiveness of OCL treatments in the studies reviewed. The most widely-used outcome scales include: (i) American Orthopaedic Foot and Ankle Society (AOFAS) score in which pain, function and alignment scores are assessed by the physician; (ii) the Visual Analogue Scale (VAS), which is a self-reported ten-point scale for pain; (iii) the Tegner scale, which is a self-reported measure of physical activity and performance, and (iv) the magnetic resonance observation of cartilage repair tissue (MOCART) score, which uses different variables to describe the constitution of the cartilage repair tissue and the surrounding structures.

The body of evidence for this review comprises two systematic reviews, two case control studies and nine case series. Majority of findings in this are from smaller size retrospective single studies which could be particularly susceptible to bias, especially patient selection. In addition there is heterogeneity in terms of study design, patient characteristics, management methods and outcome assessment. The two systematic reviews included suffer from significant limitations in the methodology and lack of good quality studies available for review. In summary, there is low level and inconclusive evidence for clinically effectiveness of ACI in adult patients with symptomatic osteochondral lesions of the talus. The current evidence is unable to establish the superiority of ACI to existing treatment options currently available for these patients. There is no evidence available on cost effectiveness of ACI.

1. Is ACI (first, second and third generation) clinically effective in adult patients with symptomatic osteochondral lesions of the talus?

Niemeyer et al. (2012) systematically reviewed 16 retrospective studies to conclude an overall clinical success rate of 89.9% with limited clarity on the basis of this finding. Giannini et al. (2014), a retrospective case study with 46 patients, reported overall success rate was 93.5% at 7 years follow up with significant improvements in AOFAS from a mean pre-operative score of 57.2 ±14.3 to 86.8 ±13.4 at the 12-month follow up, and results continued to improve after three and seven years. A prospective case series with 18 patients, reported (50.3% ±13.2%) improvement in all clinical scores (FFI, AOFAS, MOCART and AAOS) 21 months after matrix-associated chondrocyte implantation (MACI) (Aurich et al., 2011).

Another recent retrospective case series (Kwak et al. 2014) reported the clinical outcomes of first generation ACI from 32 consecutive patients who had previously failed bone marrow stimulation, supporting the claim that ACI produced significant improvements in AOFAS score, Tegner activity score, and the Finsen score over a 70-month follow-up period. Magnan et al. (2012) investigated the effectiveness of MACI in a case series of 30 patients operated by a single surgeon, reporting significant improvement in AOFAS and VAS scores after 3 years follow-up.

Severe limitations of the studies including in the review especially potential for patient selection bias, lack of a comparator arm and heterogeneity of the study populations, are likely to significantly impact replication of these findings in a real-world setting.

While studies included in this review suggest that autologous chondrocyte implantation (ACI) is clinically effective in the treatment of OCL of talus, the extent of ACI's clinical effectiveness only becomes meaningful in the context of existing treatments or emerging technologies. Zengerink et al., 2010 included 52 studies in a systematic review of all OCL of talus treatments, totalling 1361 patients. In this study, ACI had an overall success rate of 76%. However, the authors reported better overall success rates for OATS (87%) and BMS (85%). The statistical significance of the reported difference was not reported. Heterogeneity across the studies and patient population was not addressed. A smaller retrospective case control study of 20

patients study reported that MACT and microfracture (bone marrow stimulation) were both equally effective without any significant differences in clinical outcomes. (Apprich et al., 2012)

A recent retrospective case-control study reporting comparable levels of effectiveness when ACI and BMDCT, were used to treat a homogenous patient sample (n=40 for each subgroup) with isolated osteochondral lesions of the talar (Buda et al., 2015). Both treatments were reported to produce excellent AOFAS scores postoperatively, which was further supported by clinical and radiological evaluation (e.g. using MOCART scores). However, neither of these treatments are currently considered standard interventions for OCLs of the talus.

In summary, the current evidence for clinically effectiveness of ACI in adult patients with symptomatic osteochondral lesions of the talus is inconclusive.

2. Is ACI (first, second and third generation) cost effective in adult patients with symptomatic osteochondral lesions of the talus?

The review did not identify any relevant studies on cost effectiveness of ACI used in the treatment of osteochondral lesions of the talus compared to existing treatments. In some studies, authors have expressed opinion that ACI may not be more cost effective compared to other treatments (Zengerink et al., 2010, Apprich et al., 2012, Magnan et al., 2012). However, these views are yet to be substantiated with a robust, statistically-backed evidence base.

6 Documents which have informed this Policy

NICE Technology appraisal guidance TA89: The use of autologous chondrocyte implantation for the treatment of cartilage defects in the knee, 2005.

NICE Appraisal consultation document - Autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee (including a review of TA89), March 2015.

7 Date of Review

This document will be reviewed when information is received which indicates that the policy requires revision.

References

Apprich, S.; Trattnig, S.; Welsch, G. H.; Noebauer-Huhmann, I. M.; Sokolowski, M.; Sokolwski, M.; Hirschfeld, C.; Stelzeneder, D.; Domayer, S.. Assessment of articular cartilage repair tissue after matrix-associated autologous chondrocyte transplantation or the microfracture technique in the ankle joint using diffusion-weighted imaging at 3 Tesla. Osteoarthr. Cartil. 2012;20(7):703-711.

Aurich, Matthias; Bedi, Harvinder S.; Smith, Peter J.; Rolauffs, Bernd; Mückley, Thomas; Clayton, James; Blackney, Mark. Arthroscopic treatment of osteochondral lesions of the ankle with matrix-associated chondrocyte implantation: early clinical and magnetic resonance imaging results. Am J Sports Med 2011;39(2):311-319.

Buda, Roberto; Vannini, Francesca; Castagnini, Francesco; Cavallo, Marco; Ruffilli, Alberto; Ramponi, Laura; Pagliazzi, Gherardo; Giannini, Sandro. Regenerative treatment in osteochondral lesions of the talus: autologous chondrocyte implantation versus one-step bone marrow derived cells transplantation. Int Orthop 2015;39(5):893-900.

Giannini, Sandro; Buda, Roberto; Ruffilli, Alberto; Cavallo, Marco; Pagliazzi, Gherardo; Bulzamini, Maria Chiara; Desando, Giovanna; Luciani, Deianira; Vannini, Francesca. Arthroscopic autologous chondrocyte implantation in the ankle joint. Knee Surg Sports Traumatol Arthrosc 2014;22(6):1311-1319.

Kwak, Steve K.; Kern, Brian S.; Ferkel, Richard D.; Chan, Keith W.; Kasraeian, Sina; Applegate, Gregory R.. Autologous chondrocyte implantation of the ankle: 2- to 10-year results. Am J Sports Med 2014;42(9):2156-2164.

Magnan, B.; Samaila, E.; Bondi, M.; Vecchini, E.; Micheloni, G. M.; Bartolozzi, P.. Three-dimensional matrix-induced autologous chondrocytes implantation for osteochondral lesions of the talus: midterm results. Adv Orthop 2012;2012(0):942174.

Niemeyer, Philipp; Salzmann, Gian; Schmal, Hagen; Mayr, Hermann; Südkamp, Norbert P.. Autologous chondrocyte implantation for the treatment of chondral and osteochondral defects of the talus: a meta-analysis of available evidence. Knee Surg Sports Traumatol Arthrosc 2012;20(9):1696-1703.

Zengerink, Maartje; Struijs, Peter A. A.; Tol, Johannes L.; van Dijk, Cornelis Niek. Treatment of osteochondral lesions of the talus: a systematic review. Knee Surg Sports Traumatol Arthrosc 2010;18(2):238-246.