NHS England

Clinical Commissioning Policy Proposition:

Autologous chondrocyte implantation for osteochondral lesions of the talus (adults)

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

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Plain Language Summary

The policy proposition aims to confirm NHS England's commissioning approach to autologous chondrocyte implantation (ACI) for patients with osteochondral lesions of the talus.

Cartilage covers the area where bones meet in the joints. It provides cushioning of the joint and virtually frictionless movement within the joint. Osteochondral lesions are areas of damage to this cartilage layer, that can cause pain, clicking, grinding or functional instability of the joint. Untreated lesions may progress to osteoarthritis and serious disability. The talus is one of the bones in the ankle joint and supports the weight of the body. Many patients with osteochondral lesions have experienced previous ankle trauma or injury.

Autologous chondrocyte implantation (ACI) is a procedure that was developed in the late 1980s to treat areas of cartilage damage in the knee, but has also been used in other joints including the ankle. The technique requires two surgeries: the first to harvest cartilage cells from an undamaged area of the ankle joint, which are then cultured in a laboratory to increase their number, and the second to implant the these cells into the defect. The aim is to repair the damaged area by resurfacing 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.

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

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.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether autologous chondrocyte implantation for osteochondral lesions of the talus will be routinely commissioned is planned to be made by NHS England by June 2016 following a recommendation from the Clinical Priorities Advisory Group.

2. The proposed intervention and clinical indication

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 all ACI's are two-stage procedures. 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 (‘traditional ACI’) 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.

3. Definitions

Osteochondral lesions (OCLs) or 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.

Autologous chondrocyte implantation (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.A32:N38

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: 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.

4. Aim and objectives

This policy proposition aims to define NHS England's commissioning position on autologous chondrocyte implantation (ACI) as part of the treatment pathway for adult patients with osteochondral lesions of the talus.

The objective is to ensure evidence based commissioning with the aim of improving outcomes for adults with osteochondral lesions of the talus.

5. Epidemiology and needs assessment

Osteochondral lesions (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.

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. OCL’s 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.

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).

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

6. Evidence base

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

Osteochondral lesions (OCLs) of the talus, also known as osteochondritis dissecans, are areas of joint damage involving the articular hyaline cartilage and underlying subchondral bone.

Autologous chondrocyte implantation (ACI), is a two-stage procedure involving a first surgery to harvest cartilage cells, or chondrocytes, and a second surgery to implant the cells into the damaged area with the intention of resurfacing the defect with new cartilage.

Bone marrow derived chondrocyte transplantation (BMDCT) - an emerging procedure where a scaffold loaded with mesenchymal stem cells derived from the bone marrow is transplanted in the lesion to promote healing and repair.

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.

This review of current evidence for autologous chondrocyte implantation was undertaken to answer the following questions:
Is ACI (first, second and third generation) clinically effective in adult patients with symptomatic osteochondral lesions of the talus?
Is ACI (first, second and third generation) cost effective in adult patients with symptomatic osteochondral lesions of the talus?

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 real –world setting.

While studies included in this review suggest that autologous chondrocyte implantation (ACI) is clinically effective in the treatment of talus OCL, 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 bone marrow derived cells transplantation (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 Magnetic Resonance Observation of Cartilage Repair Tissue scoring system (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.

7. Documents which have informed this policy proposition

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

8. Date of review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned (expected by June 2016).