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Protocol

Autologous chondrocyte transplantation: a phase 1 study protocol to validate the safety and feasibility of a new advanced cell therapy product for articular cartilage repair in Brazil

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ABSTRACT

Background: Membrane-assisted autologous chondrocyte transplantation is considered the gold standard surgical technique to treat greater than two millimetres diameter cartilage lesions in the knee in patients after conservative treatment failure. However, this technique is only available in developed countries of North America, Europe and Japan. According to Brazilian law, it is considered an advanced cell therapy product. There is currently no product of this type enabled for clinical use in Brazil. Following the request of the Brazilian regulatory agency (ANVISA), this phase 1 study was developed. The objective is to access feasibility and safety of a new membrane-assisted autologous chondrocyte product.
Methods: Three participants with a larger than two millimetres articular cartilage lesion in the distal femur or the patella, which did not improve their symptoms with conservative treatment, will be submitted to an arthroscopically assisted cartilage biopsy. After isolation and expansion in a good manufacturing practices facility, chondrocyte seeded collagen membranes will be surgically inserted in the lesion and fixed with fibrin glue. The follow-up period will last 1 year. Primary outcome will be incidence and severity of complications according to NCI-CTCAE version 4.0. Secondary outcomes will be Western-Ontario McMaster Universities Osteoarthritis Index scale, International Knee Documentation Committee subjective scale and magnetic resonance observation of cartilage repair tissue magnetic resonance scale.
Conclusions: This study, together with previous preclinical results and international experience, will allow patients in Latin America to have access to this advanced cell therapy.
Trial Registration: Brazilian registry of clinical trials RBR-6fgy76 (http://www.ensaiosclinicos.gov.br/rg/RBR-6fgy76/). Ethical approval: CAAE: 73911617.2.0000.0071.

Keywords: Cartilage, Pain, Knee, Regenerative medicine, Cell therapy, Chondrocytes

INTRODUCTION

Articular cartilage injuries are a public health problem, which has become more and more frequent, affecting not only the elderly, but also the economically active young population. Some epidemiological studies have estimated that these injuries can be found in 61% of all performed knee arthroscopies.[1-3]

Although it does not always cause symptoms, chondral injury has two major problems in the short term, pain, joint effusion and movement blocks can impair performance in sports activities or in manual workers. In the long run, articular cartilage injuries are considered risk factors for the development of osteoarthritis, the most frequent cause of chronic pain and joint-related disability in the adult population.[4-6] Articular cartilage is

a tissue with a unique functional architecture, capable of supporting movements in multiple planes and with multiple load conditions, enabling movement without pain. However, trauma, illness or abnormal loading conditions can damage its structure. As it is a tissue without blood or lymphatic vessels and without nerves, the healing capacity of cartilage in adults is almost zero.

Currently available treatments are not good. When subchondral bone is also affected, bleeding could promote fibrocartilagenous tissue formation inside the lesion.[7-9] Based on this principle (perforating the subchondral bone and causing bleeding), several treatment methods have been proposed in the past. Together, all the techniques that use this principle are known as "bone marrow stimulation". In fact, one of these techniques, called “microfracture”, is still the most widely used surgical method today to treat chondral lesions.[10,11] But there are two major problems: the structural properties of fibrocartilage are different from those of hyaline cartilage, which can lead to degenerative changes in the subchondral bone over time, especially in young patients and athletes. Therefore, in theory microfracture does not prevent the development of osteoarthritis, but only relieves symptoms. In addition, perforation of the subchondral bone is an aggression in itself, with its consequences, such as the formation of intralesional osteophytes. Another consequence is that if the procedure is unsuccessful and the patient continues to have symptoms, the chance of successful revision surgery using cell therapy techniques will be greatly compromised.[12-14]

Another group of procedures emerged, based on the transfer of hyaline cartilage to cover the defect. This can be achieved with the transfer of autologous osteochondral cylinders (mosaicoplasty) removed from the injured knee itself. There are three problems: first, the number of cylinders is limited because of the small donor surface. Therefore, only small, single lesions can be treated in this way.[15] Second, the removal of the cylinders causes an inflammatory response in the donor areas, which can trigger osteoarthritis. Third, this technique also injures the subchondral bone, with the consequences already mentioned above.[8,13,14] Another way to transfer hyaline cartilage to the lesion is to use homologous transplants obtained from cadavers. This technique would be indicated for larger lesions, but it has serious drawbacks: the high financial cost and bureaucratic difficulty for the installation and maintenance of a musculoskeletal tissue bank; injury to the subchondral bone for graft fixation; the possibility of non-integration of the graft in the recipient's bone and the risk of transmission of infectious diseases.[11,16]

Cell therapy could be the solution to treat cartilage lesions, specially the larger ones. In 1965, Chesterman et al was successful in isolating and expanding chondrocytes in vitro for the first time.[17] In 1982, Peterson started an experimental model in rabbits, for the treatment of articular cartilage injuries.[18] In 1984, the positive results of this model were presented in a medical congress, with 80% of the lesion being filled.[19] In 1994, the results of 23 patients operated on with this technique was published a high impact journal and started its worldwide use.[20] The technique consists of obtaining a small fragment of articular cartilage from the patient and isolating the chondrocytes, which are the cells responsible for the manufacture of the extracellular matrix of the hyaline cartilage. It is this matrix that confers the special properties of this type of cartilage. Using cell culture techniques, the number of chondrocytes in the laboratory expands, which are then implanted back into the patient's knee.

In the early days, a piece of the patient's tibial periosteum needed to be removed, to be sutured over the lesion, creating a layer under which chondrocytes in liquid medium were injected, so that they would not spread through the joint. Several publications attest to the safety and effectiveness of this procedure, to the point that today, this technique is considered the gold standard for the treatment of chondral lesions with a diameter larger than two centimeters.[21-24] The use of the periosteum has some drawbacks: the need for a second surgical incision on the tibia; handling difficulty due to retraction after withdrawal; graft delamination and loosening; graft hypertrophy. An important advance in the technique was the replacement of the periosteum with a collagen membrane.[23,25-30] With the use of the membrane, the risk of re-operation for hypertrophy decreased from 25.7% to 5%.[31] In 2014, Saris et al published the results of the European multicenter study SUMMIT, in which the chondrocytes were placed inside the porcine membrane, a technique that became known as matrix-assisted chondrocyte implantation (MACI).[32] MACI solved the problem of difficult sutures and won the microfracture in the SUMMIT study, showing that, at least in larger lesions, the chondrocyte is the gold standard treatment. In 2016, the FDA in the United States, authorized the commercial use of MACI. Since that, other countries and other similar products have been used in developed countries.

Autologous chondrocyte implantation using periosteum has already been successfully performed in patients in Brazil.[33,34] The chondrocyte culture is already well established in our service, as attested by team members' publications.[35-38] The concept was successfully tested in a large animal model.[39] However, after a consultation to the Brazilian regulatory agency (ANVISA), it was requested that, before the locally produced membrane-assisted chondrocyte could be available for a larger scale clinical use, its safety and feasibility be tested.

METHODS

Participants and setting

The Hospital Albert Einstein’s Research Ethics Committee approved this protocol (CAAE number 73911617.2.0000.0071). Orthopedic doctors of the

hospital care team will inform patients about the research. Those who show interest in participating will be scheduled for an evaluation with one of the researchers, at which time more detailed information will be provided and the informed consent form will be explained to the patient.

Inclusion criteria

Male patients, aged between 18 and 45 years-old, with or without anterior cruciate ligament injury, who present with damage to the articular cartilage in any region of the distal femur or the patella, classified as grade 2 or 3 according to the International Cartilage Repair Society (ICRS) classification, diameter greater than 2 cm^2, symptomatic and without improvement with conservative treatment based on physiotherapy, weight loss and medications.

Exclusion criteria

The exclusion criteria are superficial chondral lesion (ICRS grade 1 classification); subchondral bone injury (ICRS grade 4 classification); osteoarthritis (Kellgren-Lawrence score greater than 1); misalignment of the mechanical axis of the lower limb in the frontal plane; multiple ligament injuries; previous surgery on the affected knee; non-suturing meniscal injuries; systemic inflammatory diseases; inability to adhere to the rehabilitation protocol; functional limitations due to back or hip pain; claustrophobia; metallic implants that prevent magnetic resonance imaging; obesity (BMI greater than 30); smoking; cognitive changes with inability to read, understand and sign the informed consent.

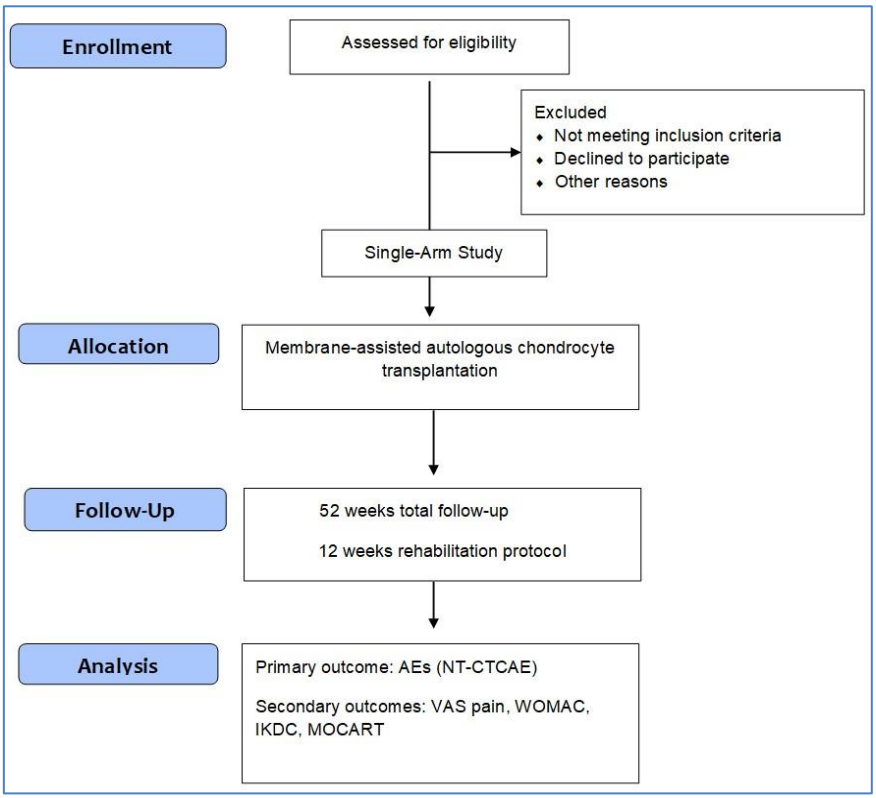

Figure 1: Flow chart of the participants through the study.

GMP=good manufacturing practices; VAS pain=verbal analogical scale of pain; WOMAC=Western-Ontario McMaster Universities Osteoarthritis Index; IKDC=International Knee Documentation Committee; MOCART=magnetic resonance observation of cartilage repair tissue.

Interventions

The study steps are summarized in Figure 1.

First surgery

Arthroscopically assisted cartilage biopsy

To obtain cartilage fragments, the patient will be submitted to arthroscopy of the injured knee under spinal anesthesia. Three fragments with five millimeters length (100 to 200 mg) will be collected from the articular cartilage in the intercondilar notch, with an arthroscopic open curette.

Autologous human serum

During the first surgery, 200 ml of the patient's own blood will be collected in the operating room, in a bag without anticoagulant. This blood will be sent to the

blood bank and the patient's autologous serum (70 ml) is extracted. This serum will be added to the culture medium at a concentration of 20% to stimulate cell expansion.

Chondrocyte isolation and expansion

The cartilage fragments obtained from the biopsy will be transferred to the good manufacturing practices room at the cell therapy laboratory inside the hospital, in a sterile Falcon tube containing cold saline (NaCl 0.9%) and antibiotics (penicillin, streptomycin and amphotericin B, Gibco).

Chondrocyte isolation will be performed following the protocol previously described by Chesterman et al.[17] Briefly, the cartilage will be fragmented and the fragments will be washed three times in culture medium containing: Ham's-F12 culture medium (Gibco) supplemented with 50 µg/ml L-ascorbic acid (Sigma), 1% antibiotic solution. antimycotic (penicillin, streptomycin and amphotericin B, Gibco), and 1% L-glutamine solution (Gibco). Fragmented cartilage will be digested in collagenase type I solution (Sigma) for approximately 16 hours at 37 °C. Thereafter, the cell suspension will be filtered using a 25 µm diameter sterile pore filter, washed three times and the cells counted in the scepter (millipore) automated apparatus. Cells will be seeded in culture medium containing 20% autologous human serum at a density of 5,000 to 10,000 cells per cm^2 in flasks of 25 or 75 cm^2. The culture medium will be changed twice a week. When cells reach 80% confluence approximately 1 week after sowing, cells will be removed with trypsin or EDTA solution (Gibco) and seeded in new vials (10,000 cells or cm^2) to approximately 5×10^6 cells within 2 to 3 weeks.

Cell seeding in the collagen membrane

A commercially available collagen membrane will be used (Chondrogide®, Geistlich do Brasil, São Paulo, SP) as scaffold. The membrane will be washed with saline (0.9% NaCl). Then 5×10^6 cells in culture medium will be sown on the membrane surface and incubated for 3 days for full interaction and cell-matrix adhesion. On the day of surgery, the membrane will be placed in a sealed sterile petri dish, in a thermal box with ice, to be sent to the operating room and implanted in the patient's knee. A membrane fragment will be sent to the laboratory to assess cell density and viability. Figure 2 illustrates some steps and the final appearance of the collagen matrix with chondrocytes.

Second surgery

Autologous chondrocyte transplantation

The surgical technique for performing the autologous chondrocyte implantation will be performed in the traditional way, already described and established in the literature.[18,32] Briefly, in the operating room, the patient is placed in the supine position and anesthetized preferably with spinal block. If the anesthesiologist deems it necessary, general anesthesia may be required. A tourniquet is used at the root of the thigh of the limb to be operated, with individually adjusted size and pressure. Arthrotomy is performed via a medial or lateral meniscal access, depending on the affected condyle.

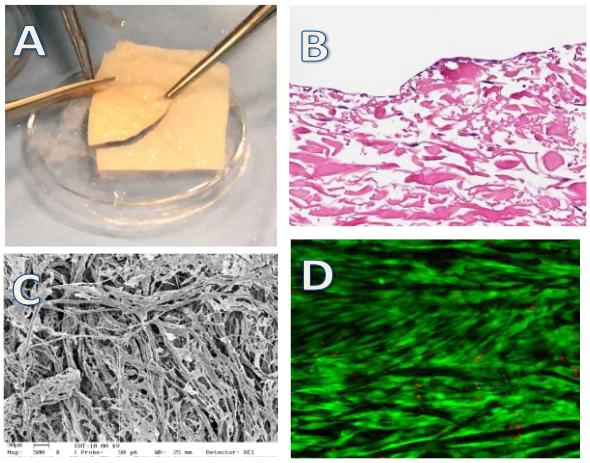

Figure 2: (A) Cell seeded collagen membrane (Chondrogide®, Geistlich do Brasil, São Paulo, SP) being cut with scissors and tweezers to adapt to the shape of the lesion; (B) conventional optical microscopy stained with H&E showing the membrane collagen fibers with attacked cells; (C) scanning electron microscopy; cell viability assay, (D) live/dead viability/cytotoxicity kit for mammalian cells (Invitrogen, Carlsbad, CA, USA) demonstrating more than 90% cell viability after three weeks expansion plus seven days seeded inside the membrane.

The chondral lesion is debrided with a bone curette, until it reaches the subchondral bone at the base of the lesion, but without causing bleeding. Debridement at the margins must be carried out until healthy cartilage is reached, keeping the vertical edges. The defect must be modeled in a geometric shape. A sterile aluminum foil mold is used to create the exact shape and size of the lesion, which will be replicated on the collagen membrane. The membrane containing the chondrocytes is fixed in the lesion with fibrin glue (Tissucol, Baxter). According to surgeon judgment, if necessary, the membrane could be also sutured over the lesion, with three or four 5-0 absorbable suture stitches (Monocryl, Ethicon). The wound is closed in layers in the usual way and the incision is covered with a dressing. Drains will not be used. Immobilization will be used just for comfort if necessary in the first two weeks after surgery.

Rehabilitation

Patients will be guided and trained during hospitalization by a physiotherapist, to walk using two crutches. They will be maintained with knee immobilizer in extension for two weeks and without load for six weeks. They will

be encouraged to practice active ankle movements, exercises to "awaken the quadriceps" with active isometric contractions. The goal is to maintain full knee extension in the first week and achieve 90 degree flexion in 6 weeks.

Hospital discharge will occur the day after surgery. The patient will have two physiotherapy sessions per week at the hospital, according to the following rehabilitation protocol: between the seventh and twelfth weeks after surgery, the load will progress to full load and the full range of motion. Between the thirteenth and the sixteenth week, strengthening, proprioception training and functional activities will be carried out. Full return to high-impact activities will only be allowed after one year of surgery, depending on the patient's symptoms and clinical tests.

Outcomes

Demographic data of patient and injury characteristics will be collected, such as age, gender, body mass index, and location of the lesion on MRI, lesion size, concomitant lesions. A complete clinical examination of gait and lower limbs will be performed before surgery and after one, two, three and six months of follow-up.

The safety of the procedure will be evaluated by the incidence of re-operations and the incidence and severity of complications according to version 4.0 of the list of the NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events) (40).

Efficacy will be assessed through clinical scales and imaging tests: VAS pain (from 0 to 10); Western-Ontario McMaster Universities Osteoarthritis Index (WOMAC) clinical scale validated for the Portuguese language; subjective IKDC clinical scale; magnetic resonance observation of cartilage repair tissue (MOCART) magnetic resonance scale.[41-43]

Follow-up

As this is a pilot study, the follow-up time will be just one year, because most adverse events occur during this period. Table 1 summarizes follow-up visits.

Statistical analysis

Descriptive statistics will be used to analyze patient's demographics, clinical characteristics, cell culture, surgical features and outcomes. Categorical data will be presented as frequency and proportion. Continuous data will be presented as median and range. All statistical analysis will be performed using IBM SPSS version 22.0 (IBM Corp, Armonk, NY, USA).

Data management and monitoring

In this research, a data monitoring committee (DMC) will be not necessary due to the short duration of the study and low risks involved for the participants. The institutional review boards (IRBs) also have responsibility for monitoring the safety of trial participants at the institution. The data monitoring will be a liability of the three main investigators according to the institution. The access of the interim results will be a duty of the main and second investigators that includes the decision to terminate the trial in any stage of the study. Any adverse event will be reported to the researchers involved and communicated to the main investigator according to the IRBs description.

Table 1: Study follow-up.

Visit	Time	Purpose
1	Pre op	Enrollment
2	Pre op	Blood collection
3	Pre op	Arthroscopically assisted cartilage biopsy
4	Day 0	MACI
5	1 weeks	AEs, VAS pain, start rehabilitation protocol
6	2 weeks	AEs, VAS pain
7	4 weeks	AEs, VAS pain
8	12 weeks	AEs, IKDC, WOMAC, finish rehabilitation protocol
9	26 weeks	AEs, IKDC, WOMAC
10	52 weeks	AEs, IKDC, WOMAC and MOCART (MRI)

AES=adverse events; PRE-OP=pre-operative visit; VAS PAIN=verbal analogical scale of pain; WOMAC=Western-Ontario Mcmaster Universities Osteoarthritis Index; IKDC=International Knee Documentation Committee; MACI= Matrix-Assisted Chondrocyte Implantation; MOCART= magnetic resonance observation of cartilage repair tissue; MRI=magnetic resonance image.

DISCUSSION

This protocol arose from the need to obtain authorization from the Brazilian regulatory agency (ANVISA) for the clinical use of an advanced cell therapy product already established and used routinely in developed countries in North America, Europe and Asia. The autologous chondrocyte, the active ingredient of this technique, is a cell obtained from the patient himself. However, the process for isolation, expansion and seeding on the collagen membrane (scaffold) may vary according to the manufacturer. Currently in Latin America, no company provides this service. For this reason, ANVISA requested that a feasibility and safety study be carried out.

Another concern regarding the use of chondrocytes in a developing country is the issue of high production costs. There is a fear that the therapy will not be cost-effective. However, studies suggest that chondrocyte trans-plantation, by preventing the progression of chondral lesions in young individuals for severe osteoarthritis and knee arthroplasty in old age, may be an advantageous strategy even for universal public health systems, such as

SUS (*Sistema Único de Saúde*) in Brazil.[44] Currently, the queues for performing hip and knee arthroplasties are the longest among all surgeries offered at SUS, and it takes more than five years for a patient to be operated. Bearing in mind that many Brazilian health insurances already offer reimbursement for the treatment of cartilage lesions with collagen membranes, we believe it is possible to offer the option with cells within a viable price, since our protocol uses relatively cheap inputs for cell expansion.

This protocol has some limitations. Due to the high cost to develop clinical studies with advanced cell therapy products, the institution chose, in agreement with ANVISA, to carry out this first feasibility study in a very small sample of only three participants. This study is unable to verify the product's effectiveness, since the sample is small and there is no control group. In the future, the data obtained and lessons learned will be applied to develop larger phase 2/3 studies to verify the effectiveness of the product.

CONCLUSION

Matrix-assisted autologous chondrocyte transplantation is the gold standard treatment for larger articular cartilage lesions. However, there is currently no product of this type enabled for clinical use in Brazil. This feasibility and safety phase 1 study will serve as the base for a future pre-market phase 2/3 randomized clinical trial, to introduce the first advanced cell therapy product for articular cartilage treatment in Brazil.

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