

CARTICEL®
(autologous cultured chondrocytes)

for Implantation

DESCRIPTION

Autologous cultured chondrocytes, the Carticel® product, are derived from *in vitro* expansion of autologous chondrocytes harvested from a patient's normal, femoral articular cartilage. Biopsies from a lesser-weight bearing area are the source of chondrocytes which are isolated, expanded through cell culture, and ultimately implanted into articular cartilage defects beneath an autologous periosteal flap. Each single use container of autologous cultured chondrocytes has approximately 12 million cells aseptically processed and suspended in 0.4 mL of sterile, buffered Dulbecco's Modified Eagles Medium (DMEM). Prior to final packaging, cell viability is assessed to be at least 80%.

CLINICAL PHARMACOLOGY

Studies have shown that implantation of the Carticel® product into the articular defect can result in the development of hyaline cartilage (see Clinical Experience). Hyaline cartilage consists of chondrocytes (≤ 5% total volume) and extracellular matrix (≥ 95% total volume). The matrix contains a variety of macromolecules, including type II collagen and proteoglycan. The structure of the matrix allows the cartilage to absorb shock and withstand shearing and compression forces. Normal hyaline cartilage also has an extremely low coefficient of friction at the articular surface. Damage to articular cartilage from acute or repetitive trauma often results in pain and disability. Partly because hyaline cartilage is avascular, spontaneous healing of large defects is not believed to occur in humans, though a variety of surgical procedures have been used in attempts to promote repair of cartilage. As cartilage heals after these procedures, fibrocartilage rather than hyaline cartilage is most commonly produced. Fibrocartilage has limited ability to withstand shock and shearing forces.

CLINICAL EXPERIENCE

Clinical information regarding the use of autologous cultured chondrocytes is available from 2 sources: 1) a series of patients treated in Sweden, and 2) a U.S. patient registry. Patients in the Swedish series received an autologous cultured chondrocyte product which was produced slightly differently than Carticel®, the U.S. product.

The series consists of 153 consecutive patients who received autologous cultured chondrocyte implantations for various defects of the knee. Clinical follow-up ranged from 1 week to 94 months. Most patients had arthroscopic evaluation; a subset had biopsy and histological evaluations. Patients presented with cartilaginous defects of the femoral condyle, patella, tibia, a combination of these, or osteochondritis dissecans, with or without non-cartilaginous defects such as anterior cruciate ligament damage requiring repair.

Following autologous cultured chondrocyte implantation, patients were routinely followed for various durations. All patients were retrospectively classified as having one of the three clinical outcomes: resumed all activities, some improvement, or no improvement. Clinical outcomes were also reported for patient subgroups including: 1) those with femoral condyle lesions who had at least 18 months of follow-up, and 2) those who failed an earlier procedure. Most patients were also assessed for arthroscopic outcomes and some patients were assessed for histological outcomes.

Clinical Outcome - Patients with Femoral Condyle Lesions

A total of 78 of 153 patients in the Swedish series had femoral condyle lesions with or without concurrent non-cartilaginous knee lesions. Patients had one or more defects ranging in size from <1-20 cm². Approximately 90% of the patients had defects of <10 cm². Clinical outcomes are shown below for 40 patients who received autologous cultured chondrocytes and were evaluable after at least 18 months of follow-up (median = 25; range = 18-94 months). In this evaluation, 70% of the patients demonstrated some clinical benefit when compared to their pre-operative condition.

Patient Response to Treatment

Defect	Resumed all activities	Some improvement	No improvement	Total
Femoral Condyle	7 (29%)	8 (33%)	9 (38%)	24
Femoral Condyle plus other Non-Cartilage Repair	4 (25%)	9 (56%)	3 (19%)	16
Total	11 (28%)	17 (42%)	12 (30%)	40

No apparent association of clinical outcomes with lesion size or cell dose could be demonstrated.

Clinical Outcome - Patients With Osteochondritis Dissecans Lesions

Clinical outcomes are shown below for 12 patients who received autologous cultured chondrocytes and were evaluable after at least 18 months of follow-up (median = 25; range = 18-94 months). In this evaluation, 83% of the patients demonstrated some clinical benefit when compared to their pre-operative condition.

Patient Response to Treatment

Defect	Resumed all activities	Some improvement	No improvement	Total
Osteochondritis Dissecans	6 (50%)	4 (33%)	2 (17%)	12

Clinical Outcome - Failed Earlier Procedures

Debridement of the cartilage defect is often performed along with Carticel® (autologous cultured chondrocytes) administration. To help differentiate the effects of the autologous cultured chondrocyte implantation procedure from those of debridement alone, an analysis was performed on 22 patients who had failed prior debridement and had a follow-up period after autologous cultured chondrocyte implantation which was greater than the time period to failure of their initial debridement. These patients had a range of cartilage defects. At the end of follow-up, 5 (23%) patients had a functional outcome rating of "resumed all activities," 8 (36%) patients had a rating of "some improvement," and 9 (41%) patients had a rating of "no improvement." Thus, 13/22 (59%) patients who had failed an earlier debridement had outcomes following autologous cultured chondrocyte implantation which were more favorable and durable than those following their earlier therapy.

Histological Outcome

Twenty-two of the initial 23 patients in the Swedish series had histological evaluation of biopsies from the transplant site. Fifteen of those patients had defects of the femoral condyle and 7 had defects of the patella. Six of the 15 femoral condyle patients showed only hyaline cartilage on their biopsy, 5 had a mixture of hyaline and fibrocartilage, and 4 had only fibrocartilage. Of the 6 patients with only hyaline cartilage on biopsy, 2 had minimal to no defects and 4 had more extensive defects (e.g., fissures, fibrillations, etc.).

Arthroscopic Outcome

Most of the 153 patients had arthroscopy. The quality of repair observed at arthroscopy correlated with the clinical outcomes. A substantial number of patients were noted at arthroscopy to have tissue hypertrophy (see Adverse Events).

Data from the US registry included 38 patients with femoral condyle lesions who received the Carticel® (autologous cultured chondrocytes) product and had at least 12 months of follow-up. Only functional outcome data were collected; no arthroscopic or histologic data are available. Although these patients were rated according to outcome measurements different from those used in the Swedish series, the results were consistent with the Swedish experience.

Two post-marketing studies are under way to evaluate the long term durability of the Carticel® repair in patients who have failed a prior surgical repair procedure. Prior surgical repair procedures are surgical interventions intended to correct cartilaginous defects such as marrow stimulation techniques, transplantation of cells or tissues, or debridement followed by an adequate rehabilitation program. Repair procedures, however, do not include lavage, biopsy, or diagnostic arthroscopy.

INDICATIONS AND USAGE

Carticel® is indicated for the repair of symptomatic, cartilaginous defects of the femoral condyle (medial, lateral or trochlear), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure.

Carticel® is not indicated for the treatment of cartilage damage associated with osteoarthritis.

Carticel® should only be used in conjunction with debridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown. Data regarding functional outcomes beyond 3 years of autologous cultured chondrocyte treatment are limited.

WARNINGS

This tissue is intended for autologous use and has not been tested for biohazards. Health providers should handle this product as if infectious agents are present.

Carticel® should not be used in patients with a known history of anaphylaxis to gentamicin. The biopsy medium used to transport the cartilage biopsies and the culture medium used during the first passage of cells contains DMEM with gentamicin. All subsequent processing is conducted aseptically and utilizes cell culture medium that does not contain gentamicin; however, trace quantities of gentamicin may still be present.

Carticel® should not be used in patients with known sensitivities to materials of bovine origin. The cell culture medium used during the culturing of the cells contains bovine serum. The medium used to package and transport the cells does not contain serum; however, trace quantities of bovine-derived proteins may still be present.

PRECAUTIONS

General

Implantation of the Carticel® product should be restricted to physicians who have completed Genzyme Tissue Repair's Surgeon Training Program.

Instability of the knee or abnormal weight-distribution within the joint may adversely affect the success of the procedure and should be corrected prior to Carticel® implantation. Abnormal varus loading of the medial compartment may jeopardize the implant. When treating

trochlear defects, abnormal patellar tracking must be corrected, if possible.

Physical activity should be resumed according to the rehabilitation plan recommended by the physician. Vigorous activity may compromise the durability of clinical benefit from Carticel[®] (autologous cultured chondrocytes). Tissue hypertrophy was an observed adverse event in clinical studies (see Adverse Reactions). Patients who develop clinical signs of tissue hypertrophy should be evaluated with arthroscopy.

Both the long-term effect of cartilage harvesting on knee function and the long term safety of cartilage implantation are unknown.

The safety of the Carticel[®] product is unknown in patients with malignancy in the area of cartilage biopsy or implant. The potential exists for *in vitro* expansion and subsequent implantation of malignant or dysplastic cells present in biopsy tissue. In addition, implantation of normal autologous chondrocytes could potentially stimulate growth of malignant cells in the area of the implant, although there have been no reported incidents in humans.

The Carticel[®] product is shipped following a preliminary sterility test with a 48 hour incubation to determine absence of microbial growth. Final (14 day incubation) sterility test results are not available at the time of implantation.

Do Not Refrigerate, Freeze, or Incubate the Carticel[®] Shipping Container or its Contents. The Carticel[®] product consists of viable, autologous cells packaged and labeled for implantation within specified time limits. The Carticel[®] transport box should be held at room temperature and remain closed until the time of implantation to ensure proper storage conditions for the cells.

Do Not Sterilize. If the Vial is Damaged or Sterility has been Compromised, Do Not Use.

Information for Patients

Patients receiving autologous cultured chondrocytes for treatment of an articular cartilage defect should receive the following information and instructions. The rehabilitation protocol provided by the physician must be closely adhered to. Early motion is very important and should start with leg supported exercises gradually increasing the number of repetitions. If pain starts to develop as the next level of activity is increased, decrease activity to the former level until the pain resolves. If exercise causes pain and/or swelling, reduce the amount of physical activity. Swelling should be controlled using ice packs. When walking for the first 6 to 7 weeks, the treated knee should be supported with two crutches. The patient should attempt to walk with a normal gait, allowing a quarter of the body weight on the treated knee for the first 3 weeks, then gradually increasing the amount of weight. At anytime during the rehabilitation process or after, if sharp pain is experienced with locking or swelling, contact the physician for medical advice.

Pediatric Use

Safety and effectiveness of Carticel[®] in pediatric populations has not been established.

ADVERSE EVENTS

General Adverse Events

Any intra-operative and post-operative complication following knee arthrotomy may occur after autologous cultured chondrocyte implantation. Of 153 patients treated with autologous cultured chondrocyte implantation in Sweden, 34 (22%) patients had the following adverse events (other than hypertrophic tissue, see below): intra-articular adhesions, 8%; superficial wound infection, 3%; hypertrophic synovitis, 3%; post-

operative hematoma, 2%; adhesions of the bursa suprapatellaris, 2%; and hypertrophic synovium, 1%. About 1% of patients developed severe adhesions resulting in "frozen knee" and requiring lysis. Adverse reactions noted at a level of less than 1% included keloid-like scar, pannus formation, significant swelling of the joint, pain with post-operative fever, and hematoma following arthroscopy.

Tissue Hypertrophy

Of 86 patients with a range of defects and at least 18 months of follow-up, 37 (43%) had hypertrophic tissue noted at follow-up arthroscopy. In those clinically evaluable patients with femoral condyle defects, 10 of 40 (25%) had some hypertrophic tissue noted at follow-up arthroscopy. The hypertrophic tissue ranged from a small amount of diffuse excess tissue at the implantation site, to a distinct ridge of tissue at the margin of the implant, to widespread excess tissue throughout the joint space. Some of these patients had clinical symptoms including painful crepitations or "catching." Symptoms generally resolved after arthroscopic resection of the hypertrophic tissue. Ten percent of patients with hypertrophy required additional treatment after hypertrophic tissue recurred following initial resection.

Registry data on 891 patients who received implantation of autologous cultured chondrocytes were derived from voluntary reporting by surgeons and do not include those from routine arthroscopy; 131 patients had a follow up of at least 18 months. After correcting for differences in follow up time, cumulative rates of patients requiring additional operative procedures were calculated; 18% of all patients required an additional procedure within 18 months and 11% of all patients required (at a minimum) shaving, trimming, debridement, or chondroplasty.

DOSAGE AND ADMINISTRATION

Patients in the Swedish series received a wide range of cell doses per cm² of defect. Available data on 70 of 78 patients with femoral condyle defects showed a median dose of 1.6 million cells/cm² of defect. The middle 80% of these patients received from 0.64 million to 3.3 million cells/cm². Each Carticel[®] (autologous cultured chondrocytes) finished product vial contains approximately 12 million cells.

Implantation of the Carticel[®] product is performed during arthrotomy and requires both preparation of the defect bed and a periosteal flap to secure the implant. Complete hemostasis must be achieved prior to periosteal fixation and cell implantation. See the Carticel[®] Surgical Manual, GTR document #65021 for instructions on performance of these procedures.

Cell Aspiration and Implantation

(For complete surgical instructions, see Surgical Manual #65021.)

NOTE:

The exterior of the Carticel[®] vial containing the cultured cells is NOT sterile. Follow strict sterile technique protocols.

When treating a defect which requires multiple vials of cells, resuspend, aspirate and inject one vial at a time.

1. Remove red plastic lid from vial. Wipe the vial surface and lid with alcohol.
2. Inspect vial contents for particulates, discoloration or turbidity. The cellular product appears as a yellowish clump in the bottom of the vial. Do not administer if contents appear turbid prior to cell suspension.
3. While holding vial in a vertical position, insert the needle of the intraspinal catheter into the vial. The needle must be positioned just above the fluid level. Slowly remove the inner needle from

the catheter, leaving flexible tip behind. Attach a tuberculin syringe to catheter.

4. Lower the catheter tip into the media and position just above the cell pellet. Aspirate all the medium from the vial leaving only the cell pellet behind. Slowly expel medium back into the vial. This action will break the cell pellet and resuspend the cells in the medium.
5. Lower the catheter tip to the base of the vial and aspirate all contents into syringe, leaving the vial empty. Slowly inject the contents into the vial again. This will assure complete suspension of the cells. Repeat these steps as needed to ensure all cells are resuspended. Cell resuspension is complete when cell particles are no longer apparent, and the medium is a consistent, "cloudy" mixture. Aspirate all contents of vial into syringe. Always hold syringe vertical to keep an air pocket at the proximal end of syringe.
6. Insert the catheter tip through the superior opening of the periosteal chamber at the site of the defect. Advance catheter to most inferior aspect of the defect.
7. Slowly inject a cell dose while moving the catheter tip from side to side and withdrawing the catheter proximally. This will ensure an even distribution of the cells throughout the defect.
8. Complete the implantation by closing the superior opening of the periosteum as instructed. See Carticel[®] (autologous cultured chondrocytes) Surgical Manual.

HOW SUPPLIED

Each vial contains approximately 12 million autologous cells for a single implantation procedure. The vial of cells is placed within secondary packaging capable of maintaining the appropriate storage temperature and cell viability for up to 72 hours. The shipping vials containing chondrocytes are accompanied by a technical data sheet with detailed specifications for the processed cells. Maintain shipping carton at room temperature.

CAUTION

Federal Law restricts Carticel[®] to sale and use by or on the order of a physician.

For more information or to obtain Genzyme Tissue Repair documents or references, contact:

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