

Rabbit Studies

- Histologic evaluations were performed at 8, 12 and 52 weeks. Improved healing of experimental defects implanted with autologous chondrocytes was observed compared to periosteal flap alone at 8, 12 and 52 weeks.

Dog Study

- Histologic evaluations were performed at 6 and 12 weeks and 12 and 18 months. Autologous chondrocytes showed improved healing compared to both empty defects and to defects covered with periosteum alone at 6 and 12 weeks. However, by the 12 and 18 month evaluations, the repair tissue had deteriorated so that no advantage of ACI over periosteum alone controls was demonstrated.

Beyond histologic variability of the defect site, no adverse tissue reaction was identified in any animals in these studies.

Post-approval Studies

Five additional large animal, post-approval studies were performed.

Goat Studies

- Three of four goat studies were 16 weeks in duration. In the fourth study, the goats were sacrificed immediately after periosteal membrane placement. Despite difficulty in postoperative management of goats and resulting subchondral plate collapse in some animals in the 16-week studies, results from all four studies suggested that chondrocytes may contribute to histological repair of focal cartilage lesions. In the only bilateral joint study, serious subchondral collapse and uniformly poor repair resulted in inconclusive data. No safety issues were identified in any of these studies.

Horse Study

- The 8-week study included two experimental arms in order to model repair of cartilage lesions with or without subchondral penetration. Both models exhibited destruction/dislodgement of the periosteal flap; however, results suggested that chondrocytes may contribute to histologic repair in cartilage defects with subchondral penetration.

While the defects in all animal models exhibited highly variable repair tissue quality (resulting in only moderate histologic scores) the best repairs with implanted chondrocytes produced hyaline-like cartilage characterized by matrix predominating in type II collagen and safranin-O or toluidine blue staining proteoglycan. Chondrocyte labeling in one of the rabbit studies⁹ and in an independent study in goats by Dell'Accio et al¹⁰ demonstrated that the hyaline-like matrix in these defects was the product of the implanted autologous chondrocytes.

14. CLINICAL STUDIES

14.1 Pre-Approval Studies

Clinical information regarding the use of autologous cultured chondrocytes was obtained from 2 open-label, observational studies consisting of a series of patients treated in Sweden and the Cartilage Repair Registry. Patients in the Swedish series received an autologous cultured chondrocyte product similar to Carticel.

14.1.1 Swedish Series

The series consists of 153 patients who received autologous chondrocyte implantation for various defects of the knee. Patients presented with cartilage defects of the femoral condyle, patella, tibia, a combination of these, or osteochondritis dissecans, with or without comorbidity such as anterior cruciate ligament insufficiency requiring reconstruction.

Following autologous chondrocyte implantation, patients were followed for various durations. Clinical follow-up ranged from 1 week to 94 months; 86 patients had at least 18 months of follow-up. Most patients had arthroscopic evaluation; a subset had biopsy and histological evaluations. All patients were retrospectively classified as having one of three clinical outcomes: resumed all activities, some improvement, or no improvement. Clinical outcomes were also reported for patient subgroups including: 1) 40 patients with femoral condyle lesions, 2) 12 patients with osteochondritis dissecans lesions and 3) 22 patients who failed a prior debridement.

1) Clinical Outcome - Patients with Femoral Condyle Lesions

A total of 78 of 153 patients had femoral condyle lesions with or without co-morbidity. Patients had one or more defects ranging in size from < 1–20 cm². Of the patients with femoral condyle lesions, 40 were evaluable after at least 18 months (median = 25; range = 18 to 94 months). Clinical outcomes for the 40 patients are summarized in **Table 5**.

Table 5: Patient Response to Treatment

Defect	Resumed All Activities	Some Improvement	No Improvement	Total Patients
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

2) Clinical Outcome – Patients With Osteochondritis Dissecans Lesions

Of the 12 patients who received autologous cultured chondrocytes for treatment of an osteochondritis lesion, 6 of the 12 had “resumed all activities,” 4 had “some improvement” and 2 had “no improvement” after the 18-month (median = 25; range = 18-94 months) follow-up period.

3) Clinical Outcome – Failed Earlier Procedures

Debridement of the cartilage defect is often performed along with administration of autologous cultured chondrocytes. 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 at least as long as the time period to failure of their initial debridement. At the end of follow-up, 5 of the 22 patients had a functional outcome rating of “resumed all activities.” 8 of the 22 patients had a rating of “some improvement” and 9 of the 22 patients had a rating of “no improvement.” Thus, 13 of the 22 patients (59%) who had failed an earlier debridement had outcomes that were more favorable and durable following autologous cultured chondrocyte implantation than their previous debridement without cells.

Histological Outcome

Twenty-two (22) patients in the Swedish series had histological evaluation of biopsies from the implant site one or more years after their autologous chondrocyte implantation. Fifteen (15) of those patients had defects of the femoral condyle and 7 had defects of the patella. Six (6) of the 15 femoral condyle biopsies showed hyaline-like cartilage, 5 had a mixture of hyaline and fibrocartilage, and 4 had only fibrocartilage. Of the 6 biopsies with hyaline-like cartilage, 2 had minimal to no surface irregularities and 4 had some surface irregularities (e.g., fissures, fibrillations, etc.).

Arthroscopic Outcome

As an objective outcome evaluation, 86 of the 153 patients had a follow-up arthroscopy for investigational purposes at 18 months or more post-implantation. In some cases, the quality of repair observed at arthroscopy was considered to be supportive of the clinical or functional outcomes. A substantial number of patients were noted at arthroscopy to have tissue hypertrophy [see *Adverse Reactions (6)*].

14.1.2 Cartilage Repair Registry

The Cartilage Repair Registry (CRR) was established upon the introduction of Carticel into orthopedic practice in March of 1995. The CRR was designed to prospectively collect the clinical outcomes of Carticel and other cartilage repair treatments for chondral lesions in the knee. Clinical data were collected at baseline arthroscopy, implantation, intervals of 6 and 12 months, and annually thereafter; adverse reaction data were collected on an ongoing basis through CRR adverse reaction collection and spontaneous reporting. Inclusion in the CRR was based on a qualifying event that was defined as a knee arthroscopy in which a chondral lesion was identified and a cartilage biopsy was harvested. Participation in the CRR was voluntary, and not all patients biopsied or implanted were included. As of November 21, 1997, 891 patients had been implanted worldwide, and 644 of these patients were included in the CRR. Functional outcomes were based on responses to a modified version of the Cincinnati Knee Rating System.

Data from a subset of 191 US patients in the CRR as of December 31, 1996 who had undergone repair of lesions on the femoral condyle (medial, lateral or trochlea) were assessed to support licensure. Patients were between the ages of 15–57, 66% (126/191) were male, and 34% (64/191) were female and one patient's gender was not reported. Of these 191 patients, 38 had at least 12 months of follow-up. At study baseline, these 38 patients' mean rating of overall condition was 3.2, which is defined as fair to poor: limitations that affect activities of daily living-no sports possible. At 12 month follow-up, these patients reported an overall condition score of 6.4 defined as good: some limitation with sports but can participate if patient compensates. 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.

14.2 Post-Approval Studies

Two post-approval studies were conducted and completed as a condition of approval for Carticel: the Registry Based Study (RBS) and the Study of the Treatment of Articular Repair (STAR).

14.2.1 Registry-Based Study (RBS)

The RBS was a retrospective analysis of data collected for a cohort of 97 U.S. patients treated between March of 1995 and March of 1997. Of the 97 patients enrolled, 95% completed 1-year follow-up, 80% completed 2-year follow-up and 74% completed 3-year follow-up. Of these 97 patients, 44 were part of the subset of 191 US patients in the CRR described above. A limitation of this study is the lack of a control group. Patients included in this study had a prior non-Carticel cartilage repair procedure (e.g., debridement or marrow stimulation procedure) performed at the time of the index arthroscopy, subsequently failed this procedure and went on to receive Carticel. In the 5 years prior to the index arthroscopy for the study, this patient population had received prior knee surgeries to include: 47% (46/97) of patients had at least one debridement/lavage of a cartilage defect, 25% (24/97) of patients had a bone marrow stimulation procedure, 31% (30/97) had at least one diagnostic arthroscopy, 30% (29/97) had at least one meniscus repair/menisectomy and 10% (10/97) of patients had a ligament repair/reconstruction performed on the treated knee.

Using a modified Cincinnati Knee Rating System at study baseline, this patient population had a mean overall condition score of 3.1 defined as fair to poor: limitations that affect activities of daily living-no sports possible. Patients included were between the ages of 16–56, 69% (67/97) were male and 31% (30/97) were female. For the type of defect, 62% (60/97) of the defects were acute while 37% (36/97) were chronic. Of the treated defects, 75% (73/97) were treated on the medial femoral condyle (MFC), 26% (25/97) on the lateral femoral condyle (LFC) and 19% (18/97) on the trochlea. Adverse reactions collected during this study are provided in Adverse Reactions (6).

14.2.2 Study of the Treatment of Articular Repair (STAR)

The STAR study was an open-label within patient comparison of a prior non-Carticel (index) procedure to implantation of Carticel for articular cartilage defects of the distal femur. All patients had experienced an inadequate response to a prior non-Carticel surgical treatment, defined as both: a) patient and surgeon agreement that the patient's symptoms/function required surgical re-treatment of the defect and b) the patient's rating of the overall condition of the knee was a score ≤ 5 using the Modified Cincinnati Knee Rating System. In this patient population, the median time to meet the failure criteria was 3.4 months for the prior non-Carticel procedure and 90% of patients failed within 10.3 months. Patients who met these criteria were treated with Carticel and assessed every 6 months for up to 4 years.

Treatment failure for Carticel was defined as any of the following: a) the patient underwent surgical retreatment that violated the subchondral bone or reimplantation with Carticel for the same index defect, b) complete delamination or removal of the graft, or c) the patient's rating of the overall condition of the knee using the Modified Cincinnati Knee Rating System failed to improve from the baseline knee score over 3 consecutive 6-month intervals.

A total of 154 patients were treated with Carticel. At the index surgery required for study entry, patients had one or more of the following interventions: 120 patients (78%) had debridement, 44 patients (29%) had microfracture, 18 (12%) had subchondral drilling, 10 (6%) had abrasion arthroplasty, and 7 (5%) had an osteochondral autograft. The mean lesion size was 4.6 (± 3.2, SD) cm². Fifty patients (32%) had multiple lesions in the reference knee and 29 patients had Carticel implanted in more than one lesion. Lesions that were implanted were located on the medial femoral condyle in 109 patients, lateral femoral condyle in 32 patients and trochlea in 46 patients. Forty patients (26%) had lesions which involved osteochondritis dissecans (OCD).

Of the 154 patients treated with Carticel, 28 patients discontinued the study early. The numbers of patients completing the 24 and 48 month follow-up visits are 136 and 115, respectively. The majority of Carticel patients (N= 117) did not meet failure criteria during the study. By the end of the study, a total of 37 patients met the treatment failure criteria. Results for the 40 patients with OCD lesions were comparable to the total study population as 34 (85%) did not meet the failure criteria for the study and 6 (15%) failed treatment with Carticel. **Table 6** illustrates, during each year of follow-up, the number of patients who failed Carticel by the surgical criteria along with the number of patients who failed by the Overall Modified Cincinnati scale criteria.

Table 6: Category and Timing of Treatment Failure for Patients who Met Treatment Failure Criteria (N=37)

	1 Year	2 Years	3 Years	4 Years	Total
Patients Who Failed During the Interval	14	11	11	1	37
Surgery criteria	0	5	5	1	11
Overall Modified Cincinnati Scale criteria	14	6	6	0	26

The Overall Modified Cincinnati mean baseline score for the patient population as a whole was 3.26, poor: significant limitations that affect activities of daily living, to fair: moderate limitations that affect

activities of daily living, no sports possible. At 48 months, the mean score was 6.39, good: some limitations with sports but can participate/compensate. The improvement was statistically significant. **Table 7** shows the improvement in the Overall Modified Cincinnati score over time.

Table 7: Mean Overall Modified Cincinnati Score at Baseline and Follow-up Visits

Visit	Baseline N=154	Month 12 N=146	Month 24 N=131	Month 36 N=104	Month 48 N=101
Overall Modified Cincinnati Score ¹ Mean (SD)	3.26 (1.02)	5.58 (1.99)	5.92 (2.08)	5.87 (2.19)	6.39 (2.31)

¹ Scores are for patients who returned for follow-up. Patients who failed by score criteria are included and patients who failed by surgical criteria are excluded from the scores for timepoints after the failure criteria were met.

In addition to the change over time in activity level as measured with the Overall Modified Cincinnati Scale, there were similar and consistent changes in knee symptoms and function as measured with the Knee Injury and Osteoarthritis Outcome Score (KOOS), a measure of knee-specific symptoms and function consisting of the following five subscales: pain, symptoms, sports and recreation, knee-related quality of life, and activities of daily living. At 12 months post-Carticel implant, the mean improvement from baseline for the patient population as a whole in each subscale was as follows: pain 19 (N = 146), symptoms 15 (N = 147), sports and recreation 17 (N = 129), knee-related quality of life 18 (N = 147), and activities of daily living 18 (N = 145). At 48 months post-Carticel implant, the mean improvement from baseline was as follows: pain 24 (N = 100), symptoms 19 (N = 101), sports and recreation 31 (N = 86), knee-related quality of life 32 (N = 101), and activities of daily living 23 (N = 99).

Adverse reactions collected during this study are provided in Adverse Reactions (6).

15. REFERENCES

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16. HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

The Carticel product, NDC 58468-1025-1, consists of viable, autologous cells packaged and labeled for implantation within specified time limits. Each vial contains approximately 12 million autologous cells for a single implantation procedure.

The shipping vials containing chondrocytes are accompanied by a technical data sheet with detailed specifications for the processed cells. The vial(s) of cells is placed within secondary packaging capable of maintaining the appropriate storage temperature and cell viability for up to 72 hours.

16.2 Storage and Handling

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 Refrigerate, Freeze, or Incubate the Carticel Shipping Container or its Contents.

Do Not Sterilize.

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

17. PATIENT COUNSELING INFORMATION

Patients receiving autologous cultured chondrocytes for treatment of an articular cartilage defect should receive the following information and instructions.

- Physical activity should be resumed according to the rehabilitation plan recommended by the physician. Generally, protected weight bearing is recommended for the first 6 to 8 weeks following implantation. The patient should receive specific instructions on crutch use, ambulation and weight bearing advancement on the treated limb.
- 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.
- Patient adherence to the prescribed rehabilitation program is important and activity at variance from the rehabilitation program may compromise clinical benefit from Carticel.
- At anytime during the rehabilitation process or after, if sharp pain with locking or swelling is experienced, contact the physician for medical advice.

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