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# AUTOLOGOUS CULTURED CHONDROCYTES: ADVERSE EVENTS REPORTED TO THE UNITED STATES FOOD AND DRUG ADMINISTRATION

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**Background:** Carticel is an autologous cultured chondrocyte product that has been approved by the United States Food and Drug Administration for the repair of symptomatic cartilaginous defects of the femoral condyle that are caused by acute or repetitive trauma in patients who have been previously managed with arthroscopy or other surgical procedures. The present report describes the adverse events following Carticel implantation as reported to the Food and Drug Administration from 1996 to 2003.

**Methods:** We reviewed adverse event reports that had been submitted to the Food and Drug Administration's Med-Watch system for information on demographic characteristics, adverse events, and surgical revisions. Adverse events were categorized into sixteen non-mutually exclusive groups. Five categories were used to classify reoperations. Food and Drug Administration regulations require manufacturers to report adverse events; however, reporting by clinicians and others is voluntary. Therefore, adverse event reporting is likely to underestimate the number of event occurrences. Adverse events may be either causally or coincidentally related to the product.

**Results:** A total of 497 adverse events among 294 patients receiving Carticel were reported. The median interval from Carticel implantation to the diagnosis of an adverse event was 240 days (range, one to 2105 days). The median age of the patients was thirty-eight years, and 63% of the patients were male. Of the 270 events for which the anatomic site was noted, 258 (96%) involved the femoral condyles. More than one adverse event was reported for 135 patients (46%). The most commonly reported events were graft failure (seventy-three patients; 25%), delamination (sixty-five patients; 22%), and tissue hypertrophy (fifty-two patients; 18%). In addition, eighteen surgical site infections were reported, including eleven joint and seven soft-tissue infections. Surgical revision subsequent to Carticel implantation was mentioned in the records for 273 patients (93%). The reasons for the 389 revision procedures included graft-related problems (187 procedures; 48.1%), periarticular soft-tissue problems (ninety-seven procedures; 24.9%), and intra-articular problems (sixty-three procedures; 16.2%). Eight patients had a total knee replacement. Based on the manufacturer's reported distribution of 7500 Carticel lots between 1995 and 2002, 285 patients (3.8%) had an adverse event that was reported to the Food and Drug Administration.

**Conclusions:** The most common adverse events reported in association with the Carticel technique involved graft failure, delamination, and tissue hypertrophy.

**Level of Evidence:** Therapeutic Level IV. See Instructions to Authors for a complete description of levels of evidence.

Articular cartilage injury is common, and repair of articular cartilage defects remains one of the most challenging problems in orthopaedic surgery<sup>1</sup>. In 1743, Hunter reported that damaged cartilage is incapable of self-healing<sup>2</sup>, and subsequent experience with repair techniques has affirmed the intractable nature of these lesions. Although

many techniques such as osteochondral drilling, cartilage abrasionplasty, and microfracture have been tried, none has demonstrated long-term efficacy<sup>1,3</sup>. Beginning in the 1990s, somatic cellular therapy approaches involving autologous chondrocyte implantation and autologous osteochondral transplants (mosaicplasty) emerged as potential therapeutic

options for the treatment of cartilaginous defects of the femoral condyle. The clinical use of autologous chondrocyte implantation was first developed in Sweden<sup>4</sup>, and since 1997 the licensed product has been used in both the United States and Europe. In August 1997, Carticel, an autologous chondrocyte implantation product manufactured in the United States by Genzyme (Cambridge, Massachusetts), became the first cellular product to be licensed by the United States Food and Drug Administration. Carticel is approved for the repair of symptomatic cartilaginous defects of the femoral condyle in patients with an inadequate response to previous arthroscopic or other surgical repair procedures<sup>5</sup>. A cartilage biopsy specimen is obtained from a non-weight-bearing area in the patient's knee. Chondrocytes from the biopsy specimen are then expanded *in vitro* and reimplanted under an autologous periosteal graft that affixes the implant to the cartilaginous defect<sup>5</sup>.

Several studies have demonstrated varying clinical efficacy. Treatment failures may reflect the production of fibrocartilage, which has biomechanical properties that are inferior to those of the intended hyaline cartilage<sup>1,6,7</sup>. Three randomized, controlled trials in which autologous chondrocyte implantation was compared with traditional treatment options have been performed since the licensure of Carticel<sup>8-10</sup>. A study in which autologous chondrocyte implantation was compared with mosaicplasty demonstrated that autologous chondrocyte implantation was the superior method for the repair of articular defects in the knee<sup>8</sup>. Another study of cartilage repair of the knee joint demonstrated that osteochondral cylinder transplantation was better than autologous chondrocyte implantation because it resulted in the production of hyaline cartilage, whereas autologous chondrocyte implantation primarily produced fibrocartilage<sup>9</sup>. Knutsen et al. conducted a randomized trial in which autologous chondrocyte implantation was compared with microfracture for the treatment of cartilage defects of the knee<sup>10</sup>. They concluded that there were no histological differences between autologous chondrocyte implantation and microfracture and that both procedures were useful for short-term treatment. Several animal models have been described<sup>11-14</sup>, but only one model, involving horses, demonstrated the clinical efficacy of autologous chondrocyte implantation<sup>15</sup>. There have been few reports on the safety of autologous chondrocyte implantation<sup>4,5,14</sup>. A three-year prospective cohort study of patients undergoing Carticel implantation demonstrated adhesions, arthrofibrosis, and hypertrophic changes as the most common adverse events occurring after implantation<sup>16</sup>.

As is the case with any therapy, the anticipated benefits of autologous chondrocyte implantation must be weighed against the potential risks. The risks associated with a new technology or treatment may become apparent either before or after Food and Drug Administration approval. Post-licensure safety surveillance primarily depends on physicians, patients, manufacturers, and others to report adverse events to product manufacturers and the Food and Drug Administration's MedWatch system ([www.fda.gov/medwatch](http://www.fda.gov/medwatch)). Published surveillance summaries based on MedWatch data include reports on drugs, biological products, and blood products. Carticel

is the first Food and Drug Administration-licensed somatic cellular therapy; thus, it is especially important to monitor its safety and to communicate the surveillance data to the medical community.

### Materials and Methods

The Food and Drug Administration receives reports of adverse events following the use of approved drugs, biological products, and devices<sup>17-19</sup>. Food and Drug Administration regulations (21CFR600.80) require manufacturers to report all serious adverse events within fifteen days and others on a periodic basis. The reporting of adverse events by clinicians and others, either directly to the Food and Drug Administration or to manufacturers, is voluntary. Therefore, the number of reports of adverse events is likely to underestimate the actual number of occurrences<sup>17,20</sup>. The degree of underreporting is unknown and may vary widely by product. Likewise, reliable denominator data usually are not available; thus, the accurate calculation of adverse event "rates" is not possible. In addition, the occurrence of an adverse event during or following the administration of a pharmaceutical or biological product may represent either a coincidental or a causal association. These limitations usually preclude the inference of definite causality, but characteristics of individual reports or patterns in multiple reports have led to the detection of previously unrecognized product-associated adverse events<sup>17</sup>.

We reviewed all adverse events for which Carticel was listed as the primary suspect product as reported to the Food and Drug Administration from 1996 to 2003. To approximate the denominator, the number of patient lots distributed between 1995 and 2002 was obtained from the Genzyme Biosurgery web site<sup>21</sup>. From these adverse event reports, we discerned sixteen types of adverse events and five categories of reoperative procedures. Adverse event types were not mutually exclusive and were chosen so that we could most accurately summarize the reported adverse events on the basis of the available, and sometimes limited, information. In addition, it is frequently difficult to distinguish a possible Carticel-related adverse event from a complication associated with the preexisting condition.

### Results

Genzyme distributed 7500 lots of Carticel to physicians between 1995 and 2002<sup>21</sup>. From 1996 to 2003, 294 voluntary adverse event reports (497 adverse events) were submitted to the manufacturer and subsequently to the Food and Drug Administration. Because each Carticel lot is designated for a single patient, it is assumed that these 294 adverse event reports represent 294 patient implants. More than one adverse event was reported for 135 (46%) of the 294 patients. In this group of 294 patients, the median age was thirty-eight years (range, thirteen to sixty years), 63% of the patients were male, and 96% of the patients were United States residents. The median interval from Carticel implantation to the diagnosis of an adverse event was 240 days (range, one to 2105 days). Of the 270 events (92%) for which the anatomic site was noted, 258 (96%) involved femoral condyles and twelve (4%) involved other knee sites.

**TABLE I Characteristics of Patients with Adverse Events Related to Carticel**

Characteristic	Number of Patients (N = 294)
Age (yr)	
<20	16 (5.4%)
20-29	31 (10.5%)
30-39	118 (40.1%)
40-49	101 (34.4%)
≥50	22 (7.5%)
Unknown	6 (2.0%)
Number of reported adverse events	
1	159 (54%)
2	82 (28%)
3	41 (14%)
4	10 (3.4%)
5	1 (0.3%)
6	1 (0.3%)
Adverse events*	
Graft failure	73 (24.8%)
Delamination	65 (22.1%)
Tissue hypertrophy	52 (17.7%)
Chondromalacia	37 (12.6%)
Adhesions	37 (12.6%)
Loose bodies	28 (9.5%)
Meniscal tear	26 (8.8%)
Local infection	21 (7.1%)
Patellar maltracking	21 (7.1%)
Arthrofibrosis	16 (5.4%)
Plica formation	14 (4.8%)
Pain	4 (1.3%)
Hematoma/hemarthrosis	4 (1.3%)
Other mechanical complications†	68 (23.1%)
Other†	17 (5.8%)
Other systemic complications†	14 (4.8%)

\*Some patients had more than one adverse event; hence, the total percentage exceeds 100%. †See Appendix.

Table I shows characteristics of the 497 adverse events and the age distribution of the 294 patients. The most commonly reported adverse events were graft failure (seventy-three patients; 25%), delamination (sixty-five patients; 22%), and tissue hypertrophy (fifty-two patients; 18%). In addition, there were five reports of deep-vein thrombosis and two reports of pulmonary embolism, both of which are known potential complications of knee surgery. Three male and two female patients with ages ranging from seventeen to forty-six years had development of a deep-vein thrombosis at a median of thirteen days (range, four to seventy-five days) after Carticel implantation. Two men with ages of thirty-five and forty-seven years had development of a pulmonary embolism seven and sixteen days after Carticel implantation. Three deaths

were reported: two patients died following motor-vehicle accidents, and one died following an intracranial hemorrhage. There was not enough information in these reports to assess the potential association of these deaths with the product.

### Infections

The reports described eighteen surgical site infections, including eleven joint infections and seven superficial wound infections. Of the eleven joint infections, four were due to *Staphylococcus* species, two were due to gram-positive rods (one of which was found to be due to *Corynebacterium* species on culture), one was due to *Enterobacter cloacae*, and one was a herpes joint infection. Three infections were diagnosed clinically without microbiologic confirmation. The median time from surgery to joint infection was fourteen days (range, one to forty-nine days). Of the seven superficial wound infections, one was reported as a postoperative wound infection that occurred ten days after implantation and six were reported as being clinically consistent with cellulitis. The median time to the onset of cellulitis was 8.5 days (range, three to sixty days). All six cellulitis infections resolved with intravenous antibiotic therapy. One of the six patients with cellulitis had development of an infection following cartilage biopsy and did not undergo Carticel implantation.

### Reoperations

Of the 294 patients, 273 (93%) had 389 surgical revisions subsequent to Carticel implantation (Table II). The subsequent operative procedures were placed into one of five categories: (1) subsequent cartilage procedures, (2) periarticular soft-tissue procedures, (3) corrective intra-articular procedures, (4) resurfacing realignment procedures, and (5) aspiration, irrigation, drainage, or lavage of the joint.

Of the 389 reoperations, 187 (48.1%) involved subsequent cartilage procedures for the treatment of problems directly related to the graft. The most common types of procedures were débridement/shaving, chondroplasty, and microfracture. Ninety-seven reoperations (24.9%) were periarticular soft-tissue procedures, such as lysis of adhesions, lateral release, and synovectomy. Sixty-three reoperations (16.2%) were performed to correct an intra-articular problem. The most common corrective intra-articular procedures were removal of loose bodies (twenty-six procedures) and meniscectomy (eighteen procedures). Twenty-nine reoperations (7.5%) were performed for resurfacing or realignment, with eight patients undergoing total knee replacement. Thirteen reoperations (3.3%) were performed to cleanse the joint.

### Discussion

Our review of adverse events following the Carticel procedure that were reported to the Food and Drug Administration demonstrated that most reports described graft failure, delamination, or tissue hypertrophy. We also noted superficial and deep infections and the need for resurfacing with total knee replacement—findings that have not been previously reported, to our knowledge. However, the nature of our data on adverse

event reports does not permit a direct comparison of infection rates; the infection rate among persons receiving Carticel may be higher than, equal to, or lower than that among similar patients managed with alternative operative procedures. The adverse event reports of deep-vein thrombosis<sup>22</sup> and pulmonary embolism are important; however, emboli may be anticipated after knee procedures independent of Carticel use. Adverse events may be either causally or coincidentally related to the product or procedure.

Reconstruction of articular cartilage defects remains one of the greatest challenges in orthopaedic surgery<sup>1</sup>. Procedures intended to save a natural joint may involve correction of instability and include realignment osteotomy, removal of intra-articular loose bodies or damaged menisci (which may abrade the articular cartilage), and techniques to stimulate

articular cartilage regeneration. Many regenerative surgical procedures, such as osteochondral drilling, abrasion arthroplasty, microfracture, and chondral shaving, have had limited success<sup>1,3</sup>.

In a review of 101 patients who had been managed with autologous chondrocyte implantation, Peterson et al. reported fifty-two adverse events, including twenty-six instances of periosteal hypertrophy, seven graft failures, and three superficial wound infections<sup>4</sup>. Minas reported that five of seventy patients experienced graft failure and that twenty-six required additional surgical intervention<sup>23</sup>. These published reports portrayed fewer kinds of adverse events than our data from post-licensure surveillance. However, those reports convey incidence rate information that we cannot infer from our surveillance systems that lack complete case ascertainment.

Patients who have articular cartilage defects in the knee often have other internal joint derangements. The present report on adverse events demonstrates that, following autologous chondrocyte implantation, many patients underwent secondary procedures to correct intra-articular problems that were separate from the original cartilage reconstruction. In addition, many patients underwent procedures to address problems that were directly related to the graft.

Our conclusions are limited by the nature of spontaneous (passive) reporting systems. Adverse event reports that are submitted to the Food and Drug Administration usually are brief, focus on the event, and often do not include the patient's medical records. Other limitations include our inability to assess the appropriateness of patients selected for Carticel treatment, the type of postoperative care received, or the quality of the surgical technique. Genzyme's Biosurgery 2002 Annual Report indicated that Carticel had been used in at least 7500 patients since 1995<sup>21</sup>. Of the 294 patients described in the present report, 285 had undergone Carticel implantation through 2002, resulting in an approximate minimum adverse event-reporting rate of 3.8% (285 of 7500). As we do not have any information on the outcomes for the remaining patients who had been managed during this time-period, we are precluded from calculating an incidence rate. It is likely that this number underestimates the true frequency of adverse events because of underreporting, which is inherent in any passive surveillance system.


In summary, the present report is the first published review of adverse events among recipients of a licensed somatic cellular therapy as reported to the Food and Drug Administration. Most adverse events that were reported in association with the Carticel method involved graft failure, delamination, or tissue hypertrophy. We also identified noteworthy occurrences of joint infection. We found that this passive safety surveillance system designed for drugs and biological products can have utility for a somatic cellular therapy as well.

**TABLE II Reoperations\***

Procedure	Number of Reoperations (N = 389)
Cartilage procedures	187 (48.1%)
Débridement/shaving	85
Chondroplasty	78
Microfracture	12
Abrasion arthroplasty	4
Drilling	3
Osteochondral autograft	3
Mosaicplasty	1
Osteoarticular allograft	1
Periarticular soft-tissue procedures	97 (24.9%)
Lysis of adhesions	25
Lateral release	20
Synovectomy	15
Manipulation	12
Plica resection	12
Scar tissue removal	10
Neuroma excision	3
Corrective intra-articular procedures	63 (16.2%)
Removal of loose bodies	26
Meniscectomy	18
Patelloplasty	8
Meniscus repair	6
Anterior cruciate ligament repair	4
Posterior cruciate ligament repair	1
Resurfacing/realignment procedures	29 (7.5%)
Corrective osteotomy	15
Total knee replacement	8
Patellar realignment	6
Aspiration/irrigation/drainage/lavage	13 (3.3%)

\*The 389 reoperations were performed among 273 patients, who represented 93% of all 294 patients with reported adverse events. Some patients had more than one reoperation.

### Appendix

 Tables showing additional, infrequently reported adverse events are available with the electronic versions of this article, on our web site at [jbjs.org](http://jbjs.org) (go to the article citation

and click on “Supplementary Material”) and on our quarterly CD-ROM (call our subscription department, at 781-449-9780, to order the CD-ROM). ■

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