A Prospective Study of Autologous Chondrocyte Implantation in Patients With Failed Prior Treatment for Articular Cartilage Defect of the Knee

Results of the Study of the Treatment of Articular Repair (STAR) Clinical Trial

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Background: This is a prospective clinical study to assess the effectiveness of autologous chondrocyte implantation in patients who failed prior treatments for articular cartilage defects of the knee.

Hypothesis: Autologous chondrocyte implantation provides clinical benefit in patients with failed articular cartilage treatments.

Study Design: Cohort study; Level of evidence, 2.

Methods: One hundred fifty-four patients with failed treatment for articular cartilage defects of the knee received autologous chondrocyte implantation in a multicenter, prospective study. Follow-up was 48 months. Outcomes included change from baseline in knee function, knee pain, quality of life, and overall health. Duration of benefit after autologous chondrocyte implantation was compared with the failed prior non–autologous chondrocyte implantation procedure. Safety information was recorded. Additional analyses were performed on the 2 major cohorts of prior procedures entered into the study, marrow-stimulation technique or debridement alone, to assess if there were any significant differences in baseline characteristics, outcomes, or prognosis between the 2 groups.

Results: One hundred twenty-six patients (82%) completed the protocol. Seventy-six percent of patients were treatment successes at study end, while 24% were deemed treatment failures. Preoperative mean knee pain score was 3.0 (SD, 1.8; 0 = severe, 10 = normal). Mean improvements were observed from baseline to all time points ($P < .001$) for all outcome measures. Preoperative to 48-month values, respectively, were as follows: On the Knee injury and Osteoarthritis Outcome Score subscales of pain: 48.7 to 72.2; other symptoms: 51.8 to 70.8; sports/recreation: 25.8 to 55.8; knee quality of life: 20.9 to 52.2; and activities of daily living: 58.6 to 81.0; on the Modified Cincinnati Overall Knee score: 3.3 to 6.3; on the visual analog scale: 28.8 to 69.9; and on the SF-36 Overall Physical Health: 33.0 to 44.4. Results did not differ between patients whose primary surgery had been

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a marrow-stimulating procedure and those whose primary procedure had been a debridement alone. The median difference in duration of benefit between autologous chondrocyte implantation and the failed non–autologous chondrocyte implantation prior procedure was at least 31 months ($P < .001$). Seventy-six patients (49%) had subsequent surgical procedure(s), predominantly arthroscopic. Need for a subsequent surgical procedure was not predictive of failure.

Conclusion: Patients with moderate to large chondral lesions with failed prior cartilage treatments can expect sustained and clinically meaningful improvement in pain and function after autologous chondrocyte implantation. The subsequent surgical procedure rate observed in this study (49% overall; 40% related to autologous chondrocyte implantation) appears higher than generally reported after autologous chondrocyte implantation.

Keywords: articular cartilage repair; autologous chondrocyte implantation (ACI); Carticel

Since being introduced in Sweden more than 20 years ago,[3] autologous chondrocyte implantation (ACI) has gained increasing acceptance as a viable option for treatment of large symptomatic full-thickness chondral injuries. An extensive and growing evidence base indicates that ACI facilitates healing with formation of hyaline or hyaline-like cartilage and produces successful clinical outcomes in patients with large, disabling articular cartilage knee lesions.[††] Autologous chondrocyte implantation has an established role in several treatment algorithms where it is generally positioned toward the more severe end of the clinical spectrum as an important solution for patients for whom there are limited treatment options.[8,24,37] The present study uses a prospective, phase IV, multicentered design to confirm the effectiveness and safety of ACI (Carticel; Genzyme Corp, Cambridge, Massachusetts) when used for its Food and Drug Administration (FDA)–labeled indication "for the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral, or trochlea), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure (eg, debridement, microfracture, drilling/abrasion arthroplasty, or osteochondral allograft/autograft)."[6] The objective of this study is to determine whether patients with a failed prior cartilage procedure experience a positive clinical benefit with ACI and, if so, the magnitude and durability of that clinical improvement.

MATERIALS AND METHODS

Study Design and Patient Population

A prospective, longitudinal, multicenter study design was used to examine the efficacy, durability, and safety of ACI in patients with failed prior treatment for articular cartilage defects of the knee. Patients aged 18 years or older who had a documented history of at least one grade III or grade IV defect (modified Outerbridge classification)[29] located on the medial or lateral femoral condyle or trochlea were eligible for inclusion. All patients also must have had a prior non-ACI surgical procedure to treat the cartilage lesion within 3 years of providing informed consent for the study and be determined to have had an inadequate response to that prior surgery. This inadequate response was defined as the patient and the surgeon agreeing that the patient's symptoms and functional status warranted surgical retreatment of the lesion and a patient-reported overall knee condition of 5 or less on the Modified Cincinnati Knee Rating System[5,21,29,30] at the time of consent. It was assumed that 3 years was a sufficient and practical time period over which to evaluate the results of the prior procedures. Patients were excluded from the study if they had any of the following: previous ACI treatment on the ipsilateral knee, a history of total meniscectomy or required concurrent total meniscectomy, grade III or grade IV defects on areas other than the medial or lateral femoral condyle or the trochlea, or widespread osteoarthritis or inflammatory arthritis in the involved knee. A history of anaphylaxis to gentamycin or any products used in the preparation of autologous cultured chondrocytes also led to exclusion.

Figure 1 is a schematic representation of the study design. Patient-specific and defect-specific baseline information was captured at the time of determination that the patient was an appropriate study candidate. After ACI, patients were followed prospectively, returning for 8 follow-up visits at 6-month intervals for an overall follow-up period of 4 years. Figure 2 summarizes patient screening and study flow. The first patient entered the study in April 2000; the last patient completed the study in December 2005.

This study was designed in consultation with the FDA and was conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP). Each study site obtained Institutional Review Board approval, and all patients underwent a comprehensive informed consent process before enrollment. Data were collected via detailed case report forms, and an independent third party monitored the data for completeness and adherence to GCP.

Surgical Methods and Rehabilitation

Autologous chondrocyte implantion was performed according to standard surgical procedures described in detail elsewhere.[3,7,9,23,24,39] The cartilage biopsy specimen was sent to a single FDA-licensed facility (Genzyme Corp) where the chondrocytes were isolated from the specimen and cultured in vitro to expand the cell population in a process that is validated to maintain the chondrocyte phenotype.[2] After sterility, endotoxin, and cell viability tests according to strict manufacturing requirements, cells were shipped to the investigative site for implantation. Surgeons performed anterior cruciate ligament (ACL) repair/reconstruction, partial meniscectomy, meniscal repair, and osteotomies as necessary either during the cartilage biopsy or during ACI procedures. All patients were

[††]References 1, 3, 5, 9, 11, 21, 22, 23, 25, 27, 28, 31-33.

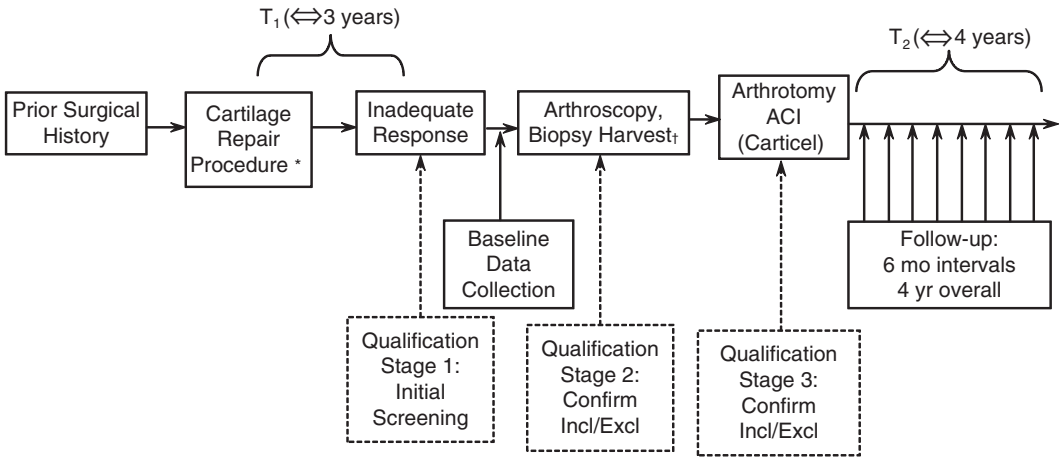

Figure 1. Schematic of study design. All patients must have had an inadequate response to non-Carticel surgical treatment of a grade III/IV defect of the medial or lateral femoral condyle or trochlea within 3 years of initial screening. Confirmation of chondral injury and defect characteristics relative to entry criteria was obtained before autologous chondrocyte implantation (ACI). After Carticel implantation, patients were followed at 6-month intervals for 4 years. *†See Table 2 for summary of failed prior non-ACI surgeries that led to the subsequent need for ACI, concurrent procedures done at the time of the failed prior non-ACI surgery, and concurrent procedures done at the time of ACI. Thirteen patients (8%) had their ACI biopsy harvest at the time the failed prior surgical procedure was performed. Incl: inclusion; Excl: exclusion.

instructed to adhere to the surgeon's instructions for postoperative rehabilitation.

Outcome Measures

Prospective efficacy outcome measures included change from baseline in overall knee condition, knee symptoms, activities of daily living (ADL), and overall physical health assessed by patient reporting using several outcome instruments. Specifically, the Modified Cincinnati Knee Rating System[5,21] was used to assess the overall knee condition, the Knee injury and Osteoarthritis Outcome Score (KOOS)[35] was used to evaluate the condition of the knee in 5 domains: pain, symptoms, sports and recreation ability, knee-related quality of life (QoL), and ADL. A 0 to 100-mm visual analog scale (VAS; 0 mm = severe pain, 100 mm = normal) was used to capture patient response to the question "How does your knee feel today?" (baseline) or "How does your knee feel today compared to before ACI?" (all other visits). Overall physical health assessment was obtained via the SF-36 Health Status Survey. The clinical outcomes of failed patients are included in these outcome analyses, and the 48-month results for all outcomes include data from patients declared post-ACI treatment failures. Analyses for change from baseline were performed using only paired data.

An additional endpoint was a within-patient comparison of the duration of benefit, that is, survivorship, of the ACI procedure to that of the prior non-ACI procedure. The statistical model used was a time-to-event analysis, with the event defined as treatment failure. This analysis provided an indication of the probability of success of ACI after failure of a primary procedure and provided evidence regarding the durability of improvement that might be expected with ACI as second-line therapy. The comparison of duration of benefit in this study is similar to prognostic analyses in the total joint arthroplasty literature comparing survivorship of a revision arthroplasty to the time to failure of the primary arthroplasty in the same patient population.[38] Failure of a prior procedure was defined according to the study entry criteria described above. The protocol prespecified an independent expert retrospective review to determine the time to failure for this prior knee procedure. An orthopaedic surgeon with expertise in outcomes research but with no involvement in ACI made this determination based on a structured review of operative notes and medical records for the failed prior surgery as well as a patient-completed questionnaire regarding the postsurgical course. The original protocol assigned a minimum period of 3 months after the arthroscopic procedure for completion of a standard rehabilitation protocol before declaring failure of the non-ACI procedure. A more conservative analysis was also performed in which the failure date for the prior procedure was assumed to be the date the patient signed the informed consent to enter this study. Failure of ACI was defined according to both surgical and functional criteria. Specifically, a patient was declared to have failed ACI if there was surgical retreatment that violated the subchondral bone (eg, abrasion arthroplasty, microfracture, drilling, unicomparmental knee replacement, or total knee replacement), reimplantation with autologous chondrocytes, complete delamination or removal of ACI, or if the patient-reported overall knee condition score (Modified Cincinnati Knee Rating System) failed to improve from baseline during 3 consecutive postoperative 6-month intervals. For patients who failed by surgical criteria alone, the time-to-treatment failure (TTF) was calculated from the date of the initial ACI to the date of reoperation. For patients determined to have failed ACI on the basis of self-reported overall knee condition alone, the TTF was defined as the date of the first of the 3 consecutive failing scores.

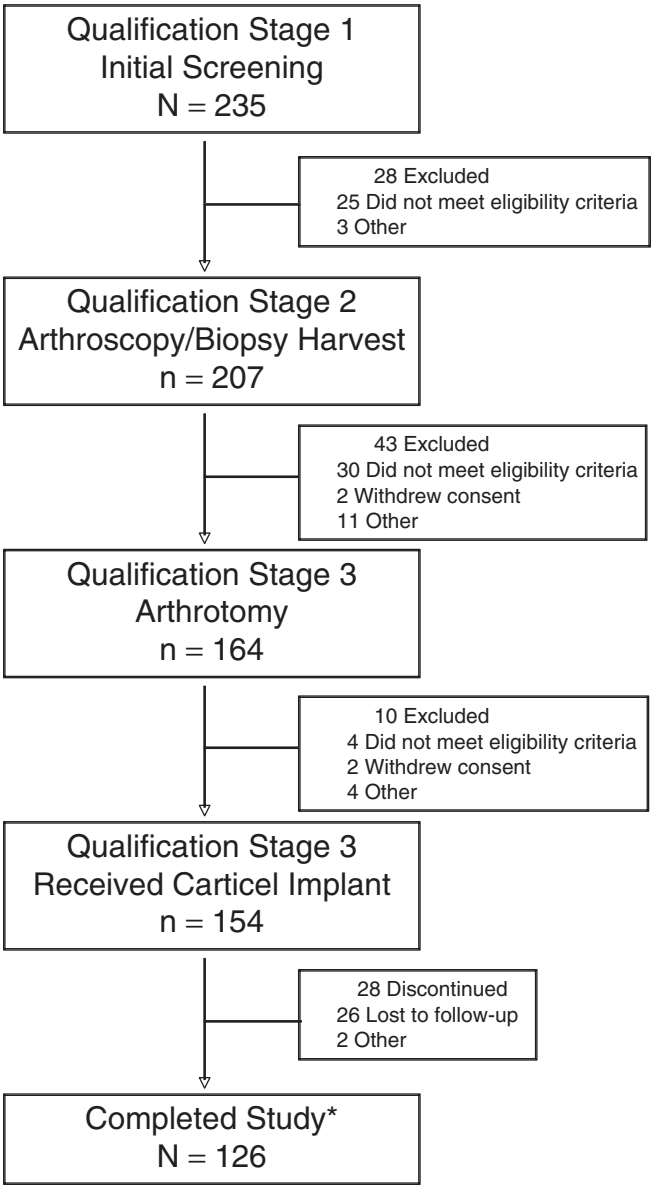

Figure 2. Patient recruitment and follow-up consort diagram. *A subset of patients consisting of the last consecutive 13 patients enrolled participated in a substudy that required only 2-year follow-up after autologous chondrocyte implantation (ACI). Ten of these substudy patients are defined as completers, having fulfilled all requirements of the substudy. Thus, 126 patients overall are defined as protocol completers, of which 116 patients completed 48-month follow-up after ACI.

For any patient determined to have failed ACI by both surgical and symptom criteria, the earlier of the 2 times was used. For all other patients, the last study visit date was used in calculation of TTF. Time-to-treatment failure for the ACI was then compared with TTF for the failed prior non-ACI procedure for each individual study patient, and summary statistics were determined for the overall study population.

In addition to the above outcome measures, safety information was systematically collected. Serious adverse events (SAEs), including subsequent surgical procedures (SSPs) and/or treatment failures after ACI, were collected at each study visit and reported via the standardized case report form. Serious adverse events were classified as mild, moderate, or severe.

This study design was determined to be optimal and appropriate given the specific objective of this study to examine the effectiveness of ACI according to its labeled indication, that is, in patients with a failed primary procedure. In this case, randomization back to a prior failed primary procedure was precluded for both ethical and practical reasons. The choice of primary treatment was made before study entry based on surgical practice. Additional analyses were performed on the 2 major cohorts of prior procedures entered into the study, marrow-stimulation technique (MST) or debridement alone, to assess if there were any significant differences in baseline characteristics, outcomes, or prognosis between the 2 groups.

Statistics

Sample size calculation was based on detecting a difference of 70% in the within-patient treatment failure rate between the failed prior procedure (100% failure rate defined by eligibility criteria) and after ACI (30% failure rate estimated based on prior clinical experience). Using a 2-sided McNemar test at $\alpha = .05$, 100 evaluable patients would provide 90% power.

Outcome measures were assessed using an intent-to-treat (ITT) analysis that included all patients who received ACI. For patient-reported outcome measures, the within-patient change from baseline to subsequent visits was determined. All statistical tests were performed by appropriate 2-sided tests with $\alpha = 0.05$.

The TTF comparison was based on a permutation test, and 95% confidence intervals (CI) were based on the Hodges-Lehmann estimate.[12,14] If a patient had not met post-ACI treatment failure criteria by the end of the 48-month follow-up period, that is, was determined a treatment success, the data were included in the analysis as "failing" at a time greater than the time interval defined by the last visit date, that is >48 months. For patients lost to follow-up, TTF was calculated using the withdrawal date in the analysis.

Serious adverse event rates were calculated and reported for the ITT population. Additional analyses of SAEs included logistic regression to evaluate possible risk factors for SSPs and the frequency and proportion of patients with SSPs that are classified as treatment failures. Events were coded using the standard Medical Dictionary for Regulatory Affairs (MedDRA, version 8.3).

All data management and statistical analyses were performed in Oracle (Oracle Corp, Redwood Shores, California), BBN/Clintrial (Bolt, Beranek, and Newman Inc, Cambridge, Massachusetts), BBN/Clintrace (Bolt, Beranek, and Newman Inc), and SAS (SAS Institute, Cary, North Carolina) as appropriate and in a validated environment.

TABLE 1
Patient Description and Baseline Characteristics[a]

Age, y, mean (SD)	34.5 (8.1)
Men	106 (69)
Women	48 (31)
Body mass index, kg/m^2, mean (SD)	27.9 (4.6)
Reason for seeking treatment	
Pain	146 (95)
Function	143 (93)
Other symptoms	98 (64)
Degree of knee pain,[b] mean (SD)	3.0 (1.82)
Overall knee condition[c]	
Poor	43 (28)
Fair	93 (60)
Good	18 (12)
Very good	0
Excellent	0
Number of lesions on index knee	
1	104 (68)
2	45 (29)
3	5 (3)
Total defect surface area at arthroscopy, cm^2, mean (SD)	5.74 (3.17)
Lesion size at arthroscopy,[d] cm^2	
<2	18 (12)
≥2 to <4	57 (37)
≥4	78 (51)
Lesion size at implant,[e] cm^2, mean (SD)	4.63 (3.20)
Lesion location[f]	
Medial	102 (67)
Lateral	27 (18)
Trochlea	24 (16)
Osteochondritis dissecans lesions	40 (26)

[a]Data are presented as n (%) unless otherwise specified (N = 154). SD, standard deviation.
[b]Degree of pain based on scale where 0 = severe, 10 = normal.
[c]Modified Cincinnati Overall Knee Condition based on a 10-point scale: poor (1, 2), fair (3, 4), good (5, 6), very good (7, 8), excellent (9, 10). To be eligible for inclusion in this study, patients had to have a Screening Modified Cincinnati Score of ≤5. All (100%) patients fulfilled this criterion.
[d]Lesion size measured at time of biopsy harvest.
[e]Mean size of lesion that qualified patient for entry into the study and which was treated with ACI.
[f]Lesion location determined at biopsy harvest. Lesion characteristic data are missing for 1 patient.

RESULTS

Treatment Characteristics

One hundred fifty-four patients received ACI and composed the primary ITT analysis population. One hundred twenty-six patients completed the study protocol (82%) (Figure 2). Mean follow-up was 45.3 (standard deviation [SD], 10.70) months; median follow-up was 48.7 months.

Patient demographic and baseline characteristics are summarized in Table 1. In general, the patients in this study were young, predominantly male, and seeking treatment for significant knee pain and decreased knee function. The majority of patients had chondral lesions ≥4 cm^2, with mean defect size at implant of 4.63 cm^2 (SD, 3.2; range, 1-30 cm^2). Fifty (32%) patients had ≥2 lesions on the study knee. Lesions were located on the medial femoral condyle (67%), lateral femoral condyle (18%), and the trochlea (16%); 40 (26% of 154) lesions were osteochondritis dissecans (OCD) lesions. On the Modified Cincinnati Knee Rating System, mean knee pain score was 3.0 (SD, 1.8; range, 0-8.0) and overall knee condition score was 3.3 (SD, 1.02). This suggests a very challenging patient population.

Table 2 summarizes the failed prior knee surgeries, concurrent procedures performed at that time, and the concurrent procedures performed at the time of ACI. Table 3 summarizes the number of surgeries as well as the number of cartilage treatment procedures performed on the study knee, before and including the failed surgery that met criteria for ACI in the study. The average number of surgeries performed on the study knee before baseline was 1.9.

Outcome Measures

All outcome measures are summarized in Table 4. The mean Modified Cincinnati Knee Rating System overall condition score at baseline was 3.3 (SD, 1.02; range, 1-5) (Table 4, Figure 3a). After 48-month follow-up, the mean score was 6.3 (SD, 2.27; range, 1-10). This change from baseline to month 48 (mean, 3.03; SD, 2.42) was statistically significant ($P < .001$) as was the change from baseline to all other time points evaluated. Categorical change from baseline to month 48 is shown in Figure 3b. At baseline, all patients had a score ≤ 5 as stipulated in the inclusion criteria, with the majority (88%) of patients having a score ≤ 4, indicating poor to fair overall knee condition at baseline. At 48-month follow-up, 77% of patients reported an overall knee condition of good to excellent (≥6).

Patient reports of knee symptoms and function (KOOS)[35] indicated significant improvements in pain, other injury-related symptoms, ability to participate in sports and recreational activity as desired, knee-related QoL, and ADL at all follow-up time points (Table 4, Figure 4). The mean improvement from baseline and from month 12 to month 48 for the 5 KOOS subscales was 23.4 (pain), 18.5 (other knee-related symptoms), 29.9 (sports and recreation), 21.8 (ADL), and 31.0 (knee QoL) ($P < .001$ in all cases).

Global VAS score was significantly improved ($P < .001$) after ACI, shown in mean (SD): baseline, 28.8 (16.44); 6-month, 60.1 (20.24); 48-month, 69.9 (25.28) (Table 4). Mean SF-36 Physical Component Summary Scale scores indicated similar improvement in physical health, shown in mean (SD): 33.0 (8.93); 12-month, 39.8 (9.72); 48-month, 44.4 (11.13) ($P < .001$ in all cases) (Table 4).

Ad hoc analyses stratified by lesion size (<2, ≥2 to ≥4, >4 cm^2), using the Modified Cincinnati Knee Rating Score and KOOS pain subdomain data, indicated in this patient population that there was no effect of lesion size on these treatment outcomes after ACI.

Survivorship Analysis

Seventy-six percent (117 patients) were treatment successes at the end of the study protocol, whereas 24% (37 patients) met the objective a priori definition of treatment failure

TABLE 2
Summary of Surgical History and Concurrent Procedures Performed[a]

Surgical Procedure Performed	ITT Population (N = 154) N (%)
Failed prior non-ACI surgery on the studied lesion, n (%)	
Debridement alone	74 (48)
Microfracture	42 (27)
Subchondral drilling	16 (10)
Abrasion arthroscopy	9 (6)
Osteochondral autograft	7 (5)
Chondroplasty	3 (2)
Marrow stimulation, unspecified	2 (1)
Other	1 (0.6)
Concurrent procedures during the failed prior non-ACI procedure, n (%)	
Loose body removal	50 (32)
Synovectomy	20 (13)
Partial meniscectomy, medial	18 (12)
Partial meniscectomy, lateral	16 (10)
Osteotomy	15 (10)
ACI biopsy harvest	13 (8)
Anterior cruciate ligament repair	11 (7)
Lateral release of patella retinaculum	9 (6)
Fixation of OCD fragment	5 (3)
Medial meniscal repair	5 (3)
Lateral meniscal repair	1 (1)
Tibial osteotomy	1 (1)
Concurrent procedures during ACI procedure, n (%)	
Tibial tubercle osteotomy	13 (8)
Lateral release of patella retinaculum	11 (7)
Other[b]	9 (6)
Tibial osteotomy	5 (3)
Posterior cruciate ligament graft reconstruction	1 (1)
Loose body removal	1 (1)
Partial meniscectomy, lateral	1 (1)
Synovectomy	1 (1)

[a]ITT, intent-to-treat; ACI, autologous chondrocyte implantation; OCD, osteochondritis dissecans.
[b]Removal of small flap of articular patella cartilage grade II 0.1 mm × 0.2 mm, hardware removal (n = 2), proximal-distal patellofemoral realignment (Elmslie-Trillant), proximal extensor mechanism reconstruction, patellae chondroplasty, debridement grade II patellae chondromalacia, bone graft to prior tibial delayed healing osteotomy, and anterior medialization–Fulkerson technique.

TABLE 3
Surgeries on the Study Knee Before Baseline[a]

Number of Surgeries Per Patient	All Prior Surgeries, n (%)	All Prior Cartilage Treatments, n (%)
1	76 (46.4)	100 (64.9)
2	39 (25.3)	41 (26.6)
3	29 (18.8)	9 (5.8)
4	6 (3.9)	2 (1.3)
5	2 (1.3)	—
6	1 (0.7)	1 (0.7)
7	1 (0.7)	—

[a]Data are presented as n (%) where the denominator is 154. The average number of surgeries and cartilage treatment procedures performed on the study knee (prior to and including the failed non-ACI surgery) was 1.9 and 1.5, respectively. One patient was determined a protocol violator for not having a cartilage treatment procedure prior to autologous chondrocyte implantation (ACI).

post-ACI. Figure 5 depicts the durability of benefit for the study population following ACI, and Table 5 lists the actual TTF for the 37 patients who failed post-ACI. The TTF for the overall study population was >46.1 months, indicating that the majority of patients maintained improvement and did not meet failure criteria by the end of the 48-month follow-up. The median TTF for the failed prior non-ACI procedures was 3.4 months according to independent reviewer assessment. This results in a median within-patient difference in the TTF for ACI versus non-ACI procedures of at least 31.7 months (95% CI: >28.2->33.8 months; $P < .001$). An additional sensitivity analysis was performed in which the date of informed consent was used as the treatment failure date for the failed prior procedure. This additional analysis resulted in a prior procedure median TTF of 8.9 months and a median within-patient difference in the TTF for ACI versus non-ACI procedures of at least 26.8 months (95% CI: >22.96->29.21 months; $P < .001$).

TABLE 4
Outcome Measures[a]

Parameter	Baseline	Month 6	Month 12	Month 24	Month 36	Month 48
Modified Cincinnati						
n	154	150	146	136	115	115
Mean (SD)	3.26 (1.02)	4.99 (1.92)	5.58 (1.99)	5.90 (2.05)	5.84 (2.14)	6.31 (2.27)
Global VAS						
n	143	136	129	112	98	96
Mean (SD)	28.8 (16.44)	60.1 (20.24)	64.4 (21.41)	68.2 (21.39)	64.4 (24.51)	69.9 (25.28)
KOOS						
Pain, n	153	n/a	147	135	114	115
Mean (SD)	48.7 (16.11)	n/a	67.0 (20.27)	70.0 (19.53)	68.8 (18.69)	72.2 (20.43)
Symptoms, n	154	n/a	147	136	115	115
Mean (SD)	51.8 (19.0)	n/a	66.9 (18.44)	68.2 (19.43)	68.0 (18.79)	70.8 (18.82)
Sports/recreation, n	141	n/a	134	127	111	110
Mean (SD)	25.8 (24.04)	n/a	44.0 (26.49)	50.6 (28.94)	51.0 (28.69)	55.8 (29.32)
ADL, n	152	n/a	147	134	114	115
Mean (SD)	58.6 (19.55)	n/a	76.0 (19.67)	80.9 (17.09)	79.4 (18.16)	81.0 (18.96)
QoL, n	154	n/a	147	136	115	115
Mean (SD)	20.9 (15.16)	n/a	38.6 (21.56)	44.6 (23.40)	44.9 (23.79)	52.2 (25.11)
SF-36 Overall Health						
n	153	n/a	146	136	115	111
Mean (SD)	33.0 (8.93)	n/a	39.8 (9.72)	42.0 (10.19)	42.5 (10.08)	44.4 (11.13)

[a]SD, standard deviation; VAS, visual analog scale; KOOS, Knee injury and Osteoarthritis Outcome Score; n/a, not applicable; ADL, activities of daily living; QoL, quality of life.

Cohort Analysis: MST Versus Debridement Before ACI

Sixty-nine patients constituted the cohort that had an MST procedure as the index lesion treatment before ACI, and 74 patients constituted the cohort that had a debridement procedure alone as the index lesion treatment prior to ACI. Table 6 summarizes baseline characteristics for these 2 cohorts. The cohorts were similar in almost every baseline variable, including baseline scores and lesion location. The mean age of the MST cohort was slightly younger than the debridement cohort, 32.9 years versus 35.5 years, respectively. Mean lesion size was virtually identical in the 2 groups, but the distribution of lesion size stratified into <2 cm^2, ≥ 2 cm^2 to <4 cm^2, or ≥ 4 cm^2 shows a trend toward a higher percentage of debridement patients (62%) than MST patients (38%) in the ≥ 4 cm^2 range. Mean changes in overall modified Cincinnati scores and KOOS scores, treatment durability, and failure rates post-ACI were compared for the 2 cohorts (Table 7). Both groups had a similar improvement in the overall Cincinnati score from baseline to 48 months, as well as similar improvements in all 5 categories of the KOOS scale. Similar proportions of patients met the a priori definition of treatment failure post-ACI, 25% (17/69) in the MST cohort and 26% (19/74) in the debridement cohort. There was no statistically significant difference in the durability of ACI after MST (>34.0 months) versus the durability of ACI after debridement (>36.4 months).

Serious Adverse Events and Subsequent Surgical Procedures

Serious adverse events, including clinically significant diagnoses noted during an SSP on the study knee, were recorded at each study visit. Table 8 lists all SAEs reported for the study knee, the majority of which were mild to moderate in severity. Because significant findings during an SSP were reported as SAEs, Table 8 includes findings at SSPs, the most common being periosteal patch hypertrophy and arthrofibrosis. Table 9 summarizes interventions during SSPs.

Eighty-four patients (54% of the overall population) experienced at least one SAE; 12 reported SAEs were not associated with SSP. Seventy-six patients (49% of 154) underwent a total of 113 SSPs on the treated knee during the course of the 4-year follow-up: 52 patients had 1 SSP, 15 patients had 2 SSPs, and 9 patients had 3 or more SSPs. For 61 patients (40% of 154), a finding during SSPs was classified as related to ACI. The majority of patients (83%; 63 of the 76 patients who had an SSP) underwent an arthroscopy or manipulation under anesthesia only.

The median time to the first SSP was 13 months, and 81% of initial SSPs were performed within 2 years of ACI. Lysis of adhesions or scar tissue removal was the most frequent initial procedure in the first 6 months; 7 of 12 patients who had an initial SSP within 6 months of ACI were treated for adhesions or scar tissue. After 6 months,

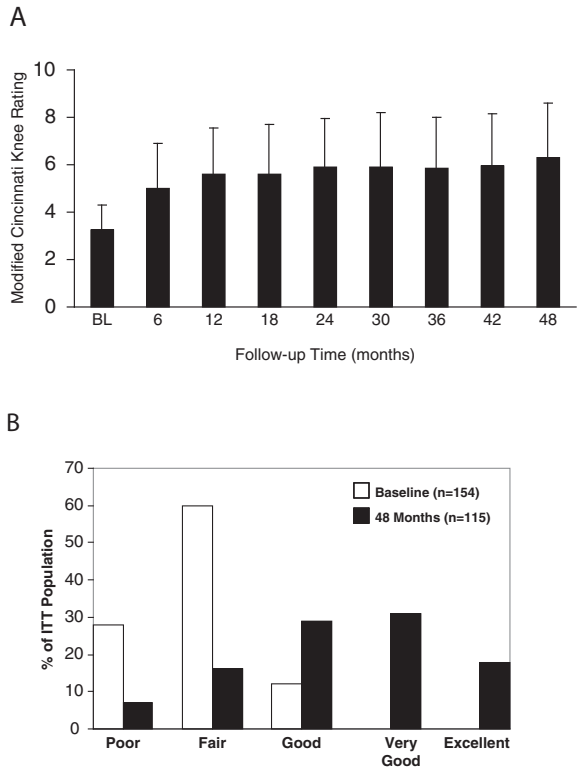

Figure 3. Modified Cincinnati Knee Rating System results. A, mean score at baseline (BL) was 3.26 ± 1.09 (SD). Change from BL was statistically significant at all time points indicating early and sustained functional improvement ($P < .001$). B, categorical representation of Modified Cincinnati Knee Rating System results. At BL, the overwhelming majority (88%) of patients indicated their knee condition was poor to fair; 12% of patients had good knee condition. At month 48, only 23% of patients evaluated their knee condition as poor to fair, while the vast majority reported that their overall knee condition was good to excellent.

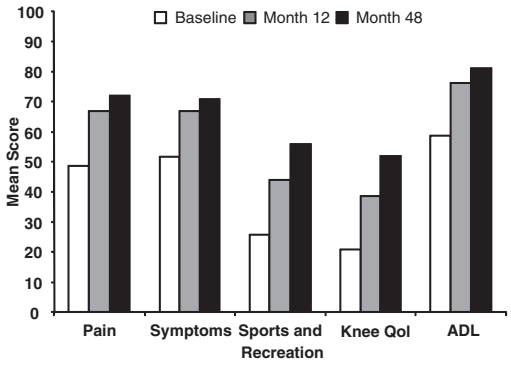

Figure 4. Knee injury and Osteoarthritis Outcome Score (KOOS) results. Data are represented as mean score for baseline, the earliest time point evaluated (12 months), and study end (48 months). The KOOS instrument consists of 42 self-administered questions in the 5 subscales depicted. The 5 subscales are scored individually via patient answers using standardized options, presented as 5 Likert boxes (scale: 0-4), for each item. The subscale item questions are summed and then transformed into a 0 (extreme knee problems) to 100 (no knee problems) for each subscale. An increase of 8 to 10 points is indicative of a clinically meaningful improvement. QoL, quality of life; ADL, activities of daily living.

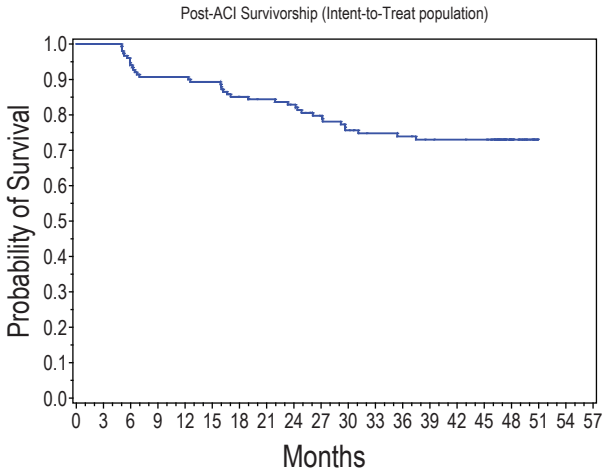

Figure 5. Kaplan-Meier representation of durability (survivorship) of autologous chondrocyte implantation (ACI) treatment for the overall study population during the 48-month follow-up period of the study. A total of 154 patients received ACI; 37 patients (24%) met a priori defined treatment-failure criteria at some point during the study (see Table 5). Overall, this challenging patient population experienced durable benefit after ACI.

debridement of cartilage lesions, including periosteal patch hypertrophy, was most frequently performed; 39 of 64 patients who had an initial SSP greater than 6 months after ACI had debridement of cartilage lesions.

Not all patients who had an SSP met the a priori definition of a treatment failure. Indeed, 61% of patients who had an SSP went on to have successful results, while 39% (30 patients) who had SSPs eventually were declared treatment failures (15 patients failed by functional score criteria, 11 by surgical criteria alone, and 4 by both score and surgical criteria as described in Materials and Methods).

Logistic regression analysis was performed on all demographic and baseline variables as predictors of SSPs. This analysis suggested that a history of ligament reconstruction might be a risk factor for SSPs after ACI (odds ratio, 2.47; 95% CI: 0.95-6.4). No association was found between a specific type of prior cartilage procedure and the occurrence of an SSP.

DISCUSSION

This study is the most extensive controlled clinical study to date in the cartilage repair field in terms of sample size, length of follow-up, and compliance with GCP. Furthermore, this study is especially distinct from other studies of cartilage repair procedures in that it prospectively defined

TABLE 5
Time-to-Treatment Failure for the 37 Patients (24%) Who Met Treatment Failure Criteria Following Autologous Chondrocyte Implantation (N = 154)

Time to Treatment Failure, mo	Patients, n (%)
0 to 6	9 (5.8)
>6 to 12	5 (3.2)
>12 to 18	8 (5.2)
>18 to 24	3 (1.9)
>24 to 30	9 (5.8)
>30 to 36	2 (1.3)
>36	1 (0.6)
Total	37 (24)

and followed a patient population with a specified stage of disease based on knee symptoms, function, and history. This was a clinically challenging group of patients who had moderate to large chondral lesions and who had failed to respond adequately to prior surgical attempts to treat their cartilage lesion. In no case was ACI the primary initial treatment of a chondral lesion; yet after ACI, the majority of patients demonstrated significant improvements from baseline in pain, other knee symptoms, knee function, and overall patient health (Modified Cincinnati Knee Rating System, KOOS, VAS, SF-36). These outcome benefits were evident at the earliest follow-up time points evaluated after ACI (6 or 12 months) and remained durable throughout the 48-month follow-up period, with 76% of patients reporting sustained improvement. These data are in agreement with outcomes from other clinical studies of ACI. For example, using a variety of outcome measures, Minas and Bryant[25] reported that 71% of patients rated overall knee outcome as good to excellent, and Mithofer et al[27] reported that 82% showed improvement in postoperative Tegner activity scores, with 72% grading knee function as good or excellent.

TABLE 6
Demography and Baseline Characteristics: Marrow-Stimulation Technique Versus Debridement Alone[a]

Characteristic	MST (n = 69)	Debridement Alone (n = 74)
Age, y, mean (SD)	32.9 (7.6)	35.5 (8.6)
Body mass index, kg/m^2, mean (SD)	28.2 (4.6)	27.9 (4.6)
Overall knee condition,[b] mean (SD)	3.2 (1.1)	3.4 (1.0)
Total defect surface area at arthroscopy, cm^2, mean (SD)	4.62 (4.1)	4.66 (2.1)
Lesion size at arthroscopy,[c] cm^2, n (%)		
<2	11 (16)	5 (7)
≥2 to <4	31 (46)	23 (31)
≥4	26 (38)	46 (62)
Lesion location, n (%)		
Medial	47 (64)	48 (68)
Lateral	11 (18)	13 (16)
Trochlea	11 (18)	13 (16)

[a]Data are presented as n (%) unless otherwise specified. SD, standard deviation.
[b]Modified Cincinnati Overall Knee Condition based on 10-point scale: poor (1, 2); fair (3, 4); good (5, 6); very good (7, 8); excellent (9, 10). To be eligible for inclusion in this study, patients had to have a Screening Modified Cincinnati Score of ≤5. All (100%) patients fulfilled this criterion.
[c]Lesion size measured at time of biopsy harvest.

The Modified Cincinnati Knee Rating System was used to assess overall knee function and knee symptoms in this study. A 2-point change in this scale is considered clinically meaningful as it represents a categorical change, for example, from fair to good.[5,21] A requirement for entry into this

TABLE 7
Clinical Outcomes: Marrow-Stimulation Technique (MST) Versus Debridement Alone[a]

	MST (n = 69)		Debridement Alone (n = 74)	
	Baseline	Month 48	Baseline	Month 48
Modified Cincinnati Overall Knee Condition				
N	69	45	74	62
Mean (SD)	3.2 (1.1)	6.4 (2.3)	3.4 (1.0)	6.2 (2.3)
KOOS				
Pain, n	68	45	74	62
Mean (SD)	49.9 (14.5)	74.6 (20.0)	48.0 (17.5)	70.8 (20.0)
Symptoms, n	69	45	74	62
Mean (SD)	53.0 (17.3)	72.7 (17.5)	51.9 (19.8)	70.1 (19.6)
Sport/Recreation, n	62	42	68	60
Mean (SD)	30.2 (27.2)	57.7 (31.0)	22.3 (19.5)	56.3 (27.8)
ADL, n	67	45	74	62
Mean (SD)	59.4 (18.1)	82.1 (19.0)	58.5 (21.0)	80.7 (18.2)
QoL, n	69	45	74	62
Mean (SD)	20.7 (15.6)	53.2 (26.2)	21.5 (14.8)	51.1 (24.0)

[a]SD, standard deviation; KOOS, Knee injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QoL, quality of life.

TABLE 8
Serious Adverse Events Reported for Study Knee[a]

Adverse Event	Severity			Total[b]
	Mild	Moderate	Severe	
Graft overgrowth (hypertrophy)	10	12	1	23 (14.9)
Arthrofibrosis	6	11	2	19 (12.3)
Cartilage injury[c]	6	10	1	17 (11.0)
Chondromalacia[d]	3	10	2	15 (9.7)
Graft complication[e]	1	13	1	15 (9.7)
Meniscus lesion	5	5	0	10 (6.5)
Graft delamination	0	6	3	9 (5.8)
Joint adhesion	4	4	0	8 (5.2)
Osteoarthritis	0	6	1	7 (4.5)
Medical device pain	4	2	0	6 (3.9)
Arthralgia	0	4	0	4 (2.6)
Synovitis	1	2	0	3 (1.9)
Chondrosis	2	1	0	3 (1.9)
Neuroma	3	0	0	3 (1.9)
Joint effusion	0	1	1	2 (1.3)
Loose body in joint	0	2	0	2 (1.3)
Tendinitis	0	2	0	2 (1.3)
Arthropathy	1	1	0	2 (1.3)
Ligament laxity	1	1	0	2 (1.3)
Exostosis	2	0	0	2 (1.3)
Joint injury	0	0	1	1 (0.6)
Wound decomposition	0	0	1	1 (0.6)
Knee deformity	0	0	1	1 (0.6)
Tendon disorder	0	0	1	1 (0.6)
Joint dislocation	0	1	0	1 (0.6)
Procedural pain	0	1	0	1 (0.6)
Osteochondrosis	0	1	0	1 (0.6)
Nerve compression	0	1	0	1 (0.6)
Panniculitis	0	1	0	1 (0.6)
Scar pain	0	1	0	1 (0.6)
Varicose vein	0	1	0	1 (0.6)
Wound infection	1	0	0	1 (0.6)
Suture-related complication	1	0	0	1 (0.6)
Hemarthrosis	1	0	0	1 (0.6)
Joint lock	1	0	0	1 (0.6)
Synovial cyst	1	0	0	1 (0.6)

[a]By study convention, findings at subsequent surgical procedures were recorded as individual serious adverse events. For example, during an arthroscopy, findings of both a torn meniscus and graft overgrowth were recorded as 2 adverse events. This table lists all reported serious adverse events for the study knee regardless of relationship to autologous chondrocyte implantation.
[b]Data are expressed as n (%) with denominator = 154.
[c]Encompasses cartilage injuries throughout the joint, for example, onset of new defects.
[d]May or may not have involved the graft site.
[e]Graft complication includes events related to the periosteal patch, graft fraying or fragmentation, and incomplete lesion filling.

study was a baseline score of ≤5 on the Modified Cincinnati Knee Rating System. In fact, 88% of patients had a score of ≤4, indicating poor to fair overall knee condition at baseline, and a more severe patient population than anticipated given this eligibility criterion for entry into the study. The change from baseline to month 48 observed in this study (3.0) is clinically meaningful and is consistent with previous studies that reported changes of 2.6,[5] 3.3,[19] and 3.8[22] after ACI. At month 48 after ACI, 77% of patients reported good to excellent overall knee condition (an overall score of 6 or better), indicating that they had no limitations in daily activities and that they had an ability to participate in sports with few/no limitations or minimal compensation.[5,21]

Evaluation of the effect of ACI on knee function and symptoms was also measured via KOOS.[35] Early and sustained improvement over baseline was reported across all 5 domains included in this instrument: pain, knee-related symptoms, sports and recreation, QoL, and ADL. An increase of 8 to 10 points in KOOS score represents clinically relevant improvement.[34] This threshold was exceeded in all domains in this study, indicating that the improvement in pain, other symptoms, and function observed

TABLE 9
Interventions During Subsequent Surgical Procedures, Regardless of Relationship, in >2% of Patients[a]

Intervention	
Debridement of cartilage lesion[b]	47 (31)
Lysis of adhesions	21 (14)
Synovectomy/synovial plica excision	19 (12)
Other debridement[c]	16 (10)
Chondroplasty	10 (6)
Meniscectomy	10 (6)
Loose body removal	7 (5)
Microfracture—index lesion	7 (5)
Scar tissue removal	7 (5)
Release of patellar retinaculum	6 (4)
Hardware removal	6 (4)
Microfracture—new lesion	6 (4)
Osteotomy	5 (3)

[a]Data are expressed as n (%) with denominator = 154.
[b]Includes debridement of index lesion and other defects.
[c]Includes debridement of other joint structures in addition to cartilage (eg, patellar fat pad).

during the course of this study was both statistically and clinically significant. These results are consistent with the positive outcomes evidenced by the Modified Cincinnati Knee Rating System. Improvement in knee-related symptoms was also evident in this study when examined by the VAS. Given the benefits to patients indicated by these 3 instruments, it is not surprising that the patients in this study reported a perception of substantial improvement from baseline in overall health (SF-36).

Despite the severity of baseline characteristics of the patients treated in this study, these results confirm a durable ACI repair as previously reported in other published reports.[‡‡] Seventy-six percent of study patients had a successful treatment outcome, that is, did not meet the predefined definition of treatment failure, at the end of the follow-up period, indicating durability of ACI treatment to 48 months. This likely represents an underestimation of the true durability of ACI as the study and patient follow-up ended at this time point. This durability of ACI treatment represents a critical improvement for the patients in this study who had limited treatment options after failing multiple non-ACI procedures and who entered the study with poor knee function. Prior reports suggest durability of ACI for up to 9[33] or 11[31] years after implantation.

Thirty-seven of 154 (24%) patients in this study were classified as treatment failures, defined as having a cartilage treatment procedure that violated the subchondral bone, reimplantation with ACI, complete delamination or removal of the graft, and/or failing to improve in overall knee condition (Modified Cincinnati Knee Rating System) from baseline during any 3 consecutive 6-month time intervals. Fifteen patients (9.7%) failed based on surgical criteria, a rate that falls well within the range (0%-24%) of treatment failure rates reported previously using surgical criteria alone.[5,19,20]

The subsequent surgical procedure rate observed in this study (49% overall; 40% related to ACI) appears higher than generally reported. Previously published SSP rates after ACI are 9.9%,[20] 16%,[22] 28%,[19] and 37%.[5] Several important factors are likely to contribute to the rate of reported SSP after ACI in this study: (1) It was done in a challenging population in that patients had complex knee injuries and had undergone multiple surgical interventions, including at least 1 cartilage treatment procedure, before entering the study; (2) patients returned for follow-up at regular and frequent visits at which their SAE/SSP information was actively solicited by study site personnel; (3) we reported all SSPs regardless of relationship to ACI; and (4) active thorough monitoring at the investigative sites, including reconciling SAE reports with source documents, ensured capture of all relevant data related to any SSP. Importantly, an SSP itself, or the need for SSP, does not constitute treatment failure. The most common cause for an SSP was periosteal patch hypertrophy. As noted in previous ACI studies, this adverse event is effectively managed arthroscopically by trimming of repair edges or hypertrophic tissue without any negative effect on cartilage growth or clinical outcome. Despite the challenging nature of the patient population in this study, the safety findings were consistent with the known safety profile of ACI currently detailed in the literature and in the ACI prescribing information.

Unlike with debridement and lavage, MST, and mosaicplasty whose indications are often limited to smaller defects,[8] it has been documented in a number of studies, including the present study, that clinical outcomes with ACI are independent of defect size.[5,13,19,21,22] Furthermore, analysis of the results by cohorts based on the 2 major types of prior procedures in this study population, MST or debridement alone, showed no significant differences in baseline characteristics or outcomes. The study results are essentially the same whether considered as a single inception cohort based on inadequate response to any primary cartilage treatment or 2 separate cohorts based on specific types of failed primary treatments. The choice of prior primary treatments is reflective of clinical practice and thus makes the results of this study generalizable. We are not aware of any well-designed study to determine the clinical superiority of debridement alone versus MST procedures as a first-line cartilage treatment or the superiority of any particular MST technique to other MST techniques, and it was beyond the objective of this study to make those types of assessments. It is an interesting and important question whether certain types of lesions, for example, large and/or very symptomatic lesions, should be considered as candidates for ACI as a first-line treatment. This question was also beyond the objective of this study. Some authors have suggested that microfracture, in particular, due to damage to the subchondral plate or other causes, may pose some risk of compromising subsequent revision surgery such as ACI.[10] This was not a finding in this study, which considered MST procedures in aggregate and was not designed to detect differences in outcomes or complications based on different subtypes of MST procedures.

An unexpected finding of this study was the short duration of benefit after the non-ACI procedures. This study was

[‡‡]References 5, 9, 21, 22, 25, 27, 28, 31-33.

designed with an interval of 3 years during which to determine failure of the prior surgical procedure, with the clear expectation that the prior procedures would have experienced longer durability than demonstrated here. Instead, the results indicate that whether using the independent reviewer's protocol-specified assessment or a conservative sensitivity analysis based on using the date of study consent as the prior procedure failure date, the median duration of prior procedure benefit was less than a year. The data from this study indicate that in this specific patient population, prior procedures failed early without proceeding to any sustained benefit in most of these patients. This provides further confirmation of the challenging nature of the lesions in the patients entered into this study. It is noteworthy that despite these challenges and previous treatment failures, more than three quarters of these patients went on to a successful result at 4 years after ACI.

Differences in study design, including entry criteria, patient population, lesion location, and evaluation methodology, make it difficult to directly compare the results of this study to those of other studies that report outcomes of other cartilage treatments such as microfracture or mosaicplasty. Foremost among these differences is that the present study specifically evaluated ACI outcomes as a second-line treatment for medial femoral condyle (MFC), lateral femoral condyle (LFC), and trochlea lesions in patients who entered the study based on rigorously predefined inclusion criteria and who had severe symptoms at baseline. In contrast, studies evaluating microfracture generally include patients undergoing initial treatment and patients with less severe baseline symptoms. For example, in a study comparing ACI and microfracture, the patient baseline symptoms were less severe than the present study and trochlea lesions were not included. Of note, despite these significant differences in the patient populations and indications evaluated, both studies found that ACI is effective across all lesion sizes, which was not true of microfracture in the Knutsen et al study.[13] Furthermore, Knutsen's conclusions are consistent with the findings of the present study: "Because microfracture is a relatively simple 1-stage procedure, it may be more suitable for a primary first-line cartilage repair of a local contained defect. In patients in whom microfracture has failed and in those with bigger, noncontained defects, autologous chondrocyte implantation may be a better option."[13(p463)]

As with the microfracture literature, mosiacplasty studies generally report on first-line, less severe patients at baseline than required by entry criteria for this study, although patients in one mosaicplasty study do appear to have some similarity to patients in this study. In a 100-patient randomized controlled trial comparing ACI and mosaicplasty, mean lesion size was 4.66 cm^2, and 94 patients had undergone previous surgical interventions.[1] Overall, 88% of the ACI patients versus 69% of the mosaicplasty patients were graded as "excellent or good result." Limitations of the Bentley et al[1] study include that, while the study showed better scores for ACI versus mosaicplasty in all outcomes evaluated, these differences were only statistically significant for one anatomic location, the medial femoral condyle. The authors' conclusions that ACI "can also dramatically reduce the symptoms of pain and disability"[1(p230)] are consistent with the results reported herein.

A weakness of the present study design is that it was not a randomized, controlled study. However, given the extensive surgical history of this population and the entry criterion requiring patients to have failed to respond to other cartilage treatments, there was insufficient justification for the investigators to repeat non-ACI procedures. The within-patient control design is an appropriate study design for a second-line indication where the possibility of randomization to a prior failed surgical procedure is precluded. In addition, there is precedence in the literature on arthroplasty revision, other areas of medicine, and in the development of therapeutic devices for use of similar study designs leading to evidence-based decisions.[16-18,36,38] Another weakness of this study is that corroborative imaging data were not collected for patients who required revision surgery. An additional potential weakness of this study was that the TTF data for the failed prior surgery was collected retrospectively by review of patient data. However, this was balanced by the strength of having this determination made by an independent data review with objective criteria. Furthermore, an additional analysis using the date of study consent as a conservative assumed date of prior treatment failure yielded similar statistical results to the prespecified analysis using the independent review data regarding differential TTF. This strengthens the overall conclusion that in this study population the durability of clinical benefit after ACI is significantly greater than the durability of clinical benefit following the prior failed procedures.

Strengths of this study design are that it was a multicenter, rigorously monitored, appropriately powered study that prospectively followed patients for 4 years after ACI via frequent clinic visits, during which multiple outcome measures were assessed, and it was appropriate to confirm the labeled indication for ACI in the United States.

In summary, all efficacy endpoints examined in this study, including TTF, Modified Cincinnati Knee Rating System, KOOS, VAS, and SF-36, consistently demonstrated statistical significance and clinically meaningful improvements after ACI. The majority of patients (76%) reported significant improvements in both symptoms and function, including recreational activities and ADL. Benefits were observed at the earliest time points evaluated and remained durable throughout the 48-month study. Subsequent surgeries for reasons related to the ACI procedure, usually graft/periosteal overgrowth or arthrofibrosis, were common but were managed arthroscopically with ultimate long-term improvement in knee pain, other knee symptoms, and function in the majority of patients. Taken together, the results of this study indicate that the majority of patients with articular cartilage injuries can expect a positive and durable outcome after treatment with ACI, even after failure of a previous non-ACI treatment. Furthermore, these results were achieved in a relatively young, active, and clinically challenging patient population that presented, on average, with severe pain and functional impairment resulting from moderate to large chondral defects. These findings support

algorithms that recommend ACI for all patients who have had inadequate response to prior treatment.[4,8,15,24]

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