A Randomized Trial of Autologous Chondrocyte Implantation Versus Alternative Forms of Surgical Cartilage Management in Patients With a Failed Primary Treatment for Chondral or Osteochondral Defects in the Knee

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Background: There are limited randomized controlled trials with long-term outcomes comparing autologous chondrocyte implantation (ACI) versus alternative forms of surgical cartilage management within the knee.

Purpose: To determine at 5 years after surgery whether ACI was superior to alternative forms of cartilage management in patients after a failed previous treatment for chondral or osteochondral defects in the knee.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: In total, 390 participants were randomly assigned to receive either ACI or alternative management. Patients aged 18 to 55 years with one or two symptomatic cartilage defects who had failed 1 previous therapeutic surgical procedure in excess of 6 months prior were included. Dual primary outcome measures were used: (1) patient-completed Lysholm knee score and (2) time from surgery to cessation of treatment benefit. Secondary outcome measures included International Knee Documentation Committee and Cincinnati Knee Rating System scores, as well as number of serious adverse events. Analysis was performed on an intention-to-treat basis.

Results: Lysholm scores were improved by 1 year in both groups (15.4 points [95% CI, 11.9 to 18.8] and 15.2 points [95% CI, 11.6 to 18.9]) for ACI and alternative, with this improvement sustained over the duration of the trial. However, no evidence of a difference was found between the groups at 5 years (2.9 points; 95% CI, −1.8 to 7.5; $P = .46$). Approximately half of the participants (55%; 95% CI, 47% to 64% with ACI) were still experiencing benefit at 5 years, with time to cessation of treatment benefit similar in both groups (hazard ratio, 0.97; 95% CI, 0.72 to 1.32; $P > .99$). There was a differential effect on Lysholm scores in patients without previous marrow stimulation compared with those with marrow stimulation ($P = .03$; 6.4 points in favor of ACI; 95% CI, −0.4 to 13.1). More participants experienced a serious adverse event with ACI ($P = .02$).

Conclusion: Over 5 years, there was no evidence of a difference in Lysholm scores between ACI and alternative management in patients who had previously failed treatment. Previous marrow stimulation had a detrimental effect on the outcome of ACI.

Registration: International Standard Randomised Controlled Trial Number: 48911177

Keywords: ACI; AMIC; microfracture; cartilage repair; knee

The true incidence of cartilage lesions of the knee is unknown. It has been observed that articular defects are present in 60% to 66% of knees undergoing arthroscopy.[7,39] It is estimated that cartilage injuries of the knee affect approximately 900,000 Americans annually, resulting in >200,000 surgical procedures.[7] Once articular cartilage is damaged, it has limited capacity to undergo repair and damage is likely to progress over time to osteoarthritis.[5,17]

The first results for autologous chondrocyte implantation (ACI) were reported in 1994, demonstrating the

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capability of an expanded cell population to re-create hyaline or hyaline-like cartilage within a chondral defect of the knee.[3] Over the past 28 years, there has been an accumulation of evidence to support its use for the treatment of cartilage defects in both the tibiofemoral[9] and the patellofemoral joints.[10]

The need for 2 surgeries, a prolonged manufacture period, and the strict regulatory requirements of delivering a cell therapy make the cost of ACI relatively high compared with some other techniques (eg, microfracture). The Australian Medical Service Advisory Committee estimates that the cost of ACI is approximately 10 times that of microfracture.[19] Consequently, its use has been restricted to geographical regions where the logistics and reimbursement make ACI a viable treatment option. Given the high costs associated with treatment, health care administrators require a high level of evidence to justify its use over established less expensive alternatives, particularly within a publicly funded health care system.

In December 2000, the National Institute for Clinical Excellence in the United Kingdom published guidance on the use of ACI for full-thickness cartilage defects in knee joints (Technology Appraisal Guidance No. 16).[22] ACI was not recommended for routine primary use in the treatment of articular cartilage defects of the knee joint within the UK National Health System (NHS). The guidance also recommended an adequately powered, randomized trial comparing ACI against the best alternative treatment for patients who had had a previous initial treatment that had not relieved symptoms. As a consequence of this guidance, the ACTIVE (Autologous Chondrocyte Transplantation/Implantation Versus Existing treatments) trial was devised with the aim of determining if ACI was effective in the treatment of cartilage lesions within a real-world setting and contributed to the evidence base regarding its cost-effectiveness. In particular, the regulatory body at the time said there was a need to define the patient population (ie, age groups, type and size of lesion) for whom this procedure is likely to be the most beneficial, and therefore the ACTIVE randomized controlled trial (RCT) was stratified by these characteristics and subgroup analyses performed.

The ACTIVE trial was a pragmatic, multicenter, parallel-group randomized trial with the aim of determining, up to 10 years after surgery, whether ACI was superior to non–cell therapy "standard" surgical management in patients who have remained symptomatic after a previous failed treatment of a chondral or an osteochondral defect in the knee. Within this article, we present the 5-year results.

METHODS

Study Design

The ACTIVE trial, which included patients with symptomatic articular cartilage defects in the knee who had undergone previous failed treatment, was a prospective, randomized, multicenter study conducted at 27 UK and 2 Norwegian sites, with enrollment beginning in May 2004. Cartilage defects of the medial femoral condyle, lateral femoral condyle, trochlea, and patella were treated with ACI or standard treatment. The protocol and all patient documentation were approved by the North Staffordshire Main Research Ethics Committee (MREC No. 04/Q2604/10). All patients provided written informed consent before participating.

Patients aged 18 to 55 years with 1 or 2 symptomatic cartilage defects in the same compartment who had failed previous surgery of the defect(s) $\geq$6 months before recruitment were included. Index defects were International Cartilage Repair Society grade 3 or 4 (chondral or osteochondral) focal cartilage defects[18] of the medial femoral condyle, lateral femoral condyle, trochlea, or patella. Exclusion criteria included a defect >12 cm^2, ligamentous instability, total meniscectomy, untreated malalignment, osteoarthritis, inflammatory arthropathy, a history of mesenchymal tumors, and a known anaphylaxis to any product used in chondrocyte preparation.

Randomization and Masking

Patients were randomized in a 1:1 ratio to ACI or intended best alternative treatment groups using a web-based central randomization service at the University of Birmingham Clinical Trials Unit. The intended best alternative non-ACI treatment for each patient was chosen separately by the treating surgeon before randomization. A minimization algorithm was used to achieve balance between groups for the following variables that were recorded before allocation: chosen intended alternative treatment (debridement, microfracture, mosaicplasty, autologous matrix-induced chondrogenesis [AMIC], bone graft, or drilling), size of the chondral defect ($<$4, 4-8, $>$8 cm^2), age ($<$30, 30 to $<$40, 40 to $<$50, $\geq$50 years), preoperative Lysholm knee scoring scale ($<$50, 50 to $<$65, 65 to $<$84, $\geq$84), and type of defect (femoral or trochlear/patellar). Masking of the patients and clinicians was not possible because of the nature of the interventions, although the independent assessments were performed by an assessor blinded to treatment allocation.

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Procedures

Briefly, 4 types of ACI were available during the trial. The first (ACI-P; Carticel; Genzyme Biosurgery, Verigen, and OsCell) followed the technique proposed originally in 1994, where the chondrocytes were implanted under a periosteum membrane.[4] The second (ACI-C) used a porcine-derived collagen membrane (Chondro-Gide; Geistlich Ltd) instead of periosteum, implanted with Carticel, Verigen, or OsCell cultured cells. The third (Matrix-induced Autologous Chondrocyte Implantation (MACI); Genzyme Biosurgery) implanted chondrocytes cultured on a porcine-derived collagen membrane (ACI-Maix; Matricel GmbH), which was cut to the desired shape at the time of surgery. The fourth was CHONDRON (Cellontech), cultured autologous chondrocytes delivered in a 1:1 ratio with fibrin gel. The alternative arthroscopic treatments comprised (1) debridement (removal of "unstable" cartilage from the defect), (2) abrasion/drilling (after cartilage debridement, abrading, or drilling of the subchondral bone until bleeding points were visible with tourniquet released), (3) microfracture (after cartilage debridement, using an awl to punch multiple small holes in the defect, about 3-4 mm apart), (4) AMIC (after microfracture, placing a porcine-derived collagen membrane—Chondro-Gide—onto the defect to provide a scaffold for new tissue formation), and (5) mosaicplasty/osteochondral autograft (after debridement, filling the defect using osteochondral cylinders harvested from low-weightbearing areas in the knee). Confirmation of previous experience of both ACI and the intended standard treatment was a protocolized requirement, with training provided if necessary. Standardized rehabilitation protocols and patient advice leaflets, according to the type of surgery received, were provided to all participants and their physical therapists. Rehabilitation after ACI followed the OsCell protocol.[1]

Independent clinical assessments were performed by centrally trained, blinded, independent assessors during clinic visits at baseline; at 3 and 6 months; at 1, 3, and 5 years after the operation; and whenever it was decided by the surgeon that an additional procedure was required on the treated knee. Patients were advised not to reveal their treatment allocation, and the surgical wounds were obscured before assessment to prevent unblinding. Patient-reported assessments were also completed at baseline and collected annually thereafter via postal questionnaire.

Outcome Measures

The dual primary outcome measures were (1) patient self-reported Lysholm knee scale[16] (scores range from 0, the worst possible score, to 100, the best possible score) at 5 years (or the means of all annual assessments over the 5-year period if a constant treatment effect was observed) and (2) the time from surgery to cessation of treatment benefit. Cessation of benefit was calculated using a combination of the patient self-reported Lysholm scores and the outcomes from the independent assessments. These consisted of the assessor completing a Lysholm scale and also indicating whether he or she thought the patient's current status compared with preoperation was "improved" or "not improved." The patient was deemed to have cessation of benefit if 2 of the following 3 criteria were satisfied: no meaningful gain in patient self-reported Lysholm score compared with preoperative score (<4-point increase; chosen to be less than a minimal improvement defined as 0.2 SD[5]), no meaningful gain in independently assessed Lysholm score compared with preoperative score (<4-point increase), and independent assessor rating as not improved. In cases where assessments were not completed at the time of an additional procedure (eg, because of the independent assessor not being able to attend the same clinic), a judgment was made by a blinded third-party adjudication committee from the patient operative notes as to whether the patient benefit had ceased. The committee agreed in advance that a further cartilage procedure to the previous area of treatment, osteotomy, or joint replacement would be considered a treatment failure. Conversely, procedures such as debridement, chondroplasty, or divisions of adhesions were not considered a failure. Patients were given 12 months to see if their procedure was successful; those who did not experience any benefit up to and including this time were considered to have ceased benefit on day 1.

Secondary outcomes consisted of the following: the 2 independent assessor-completed components described here analyzed separately, a patient rating of the operation on a 5-point ordered Likert scale (dichotomized into "pleased with operation" and "not pleased with operation" for analysis purposes), the International Knee Documentation Committee (IKDC) subjective knee evaluation form[11] (scores range from 0 [worst response] to 100 [best response]), 3 scales of the Cincinnati Knee Rating System[30,31] (sports activity scale with scores ranging from 10 [lowest] to 100 [highest]; daily living function scale with scores ranging from 0 [lowest] to 120 ["normal, unlimited"]; and sports function scale with scores ranging from 120 ["not able to do"] to 300 ["fully competitive"]), general health-related quality of life assessed using the EuroQol EQ-5D 3 level version (EQ-5D-3L),[6] and thermometer health score (scores range from 0 [worst response] to 100 [best response]). The need for any subsequent related surgical procedures was recorded. Perioperative and postoperative serious adverse events (SAEs) were collected up to 12 months after the study intervention.

Study Oversight

Study oversight was provided by an independent trial steering committee and an independent data monitoring and ethics committee, whose annual reviews of interim data provided no reason to stop or modify the trial on the basis of pragmatic stopping criteria.

Statistical Analysis

Based on being able to detect a relative 30% reduction in cessation of benefit rate from 40% to 28% with 90% power (P =

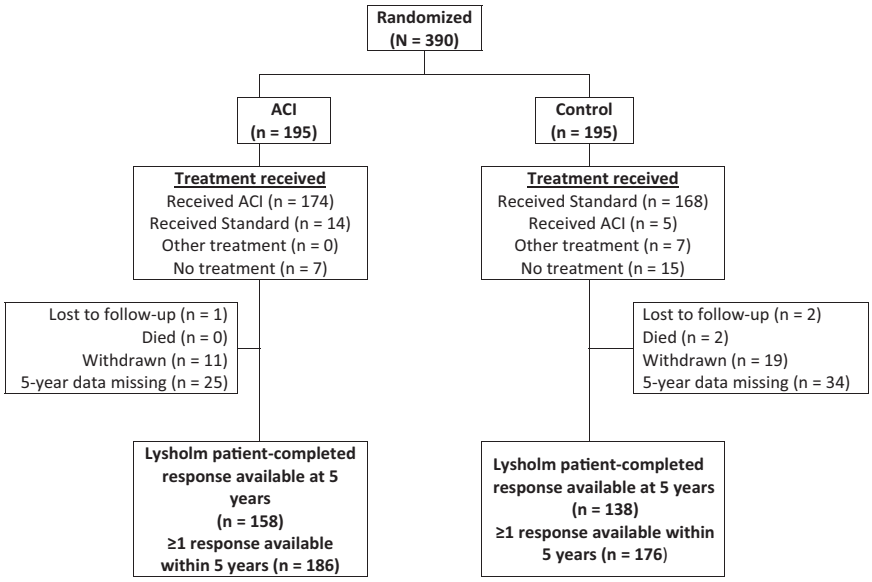

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart. ACI, autologous chondrocyte implantation.

.05) and a small—0.25 SD—difference in Lysholm score, a sample size of 660 was proposed. The study eventually closed in January 2011 after a request to cease recruitment from the funding body, with 390 patients randomized.

Analyses were intention to treat. Patient-completed Lysholm and other questionnaire responses that produce a continuous score were analyzed using a mixed linear regression model allowing for repeated assessments and adjusting for baseline score.[38] Further analyses adjusted for the minimization variables as fixed effects and recruiting center as a random effect. Treatment group $\times$ time interaction parameters were examined to see if the assumption of a constant treatment effect was appropriate. Unless this parameter was significant ($P < .05$), a single treatment effect over time was produced; otherwise, estimates at each time point were produced from the model including interaction. Time to cessation of benefit was analyzed using a Cox proportional hazards model, censoring at the date of death, withdrawal, or the last assessment provided the treatment had not already failed. A generalized estimating equation regression model[8] was used for the binary responses. Treatment $\times$ subgroup interaction was investigated by including this parameter in the linear regression model used to analyze patient-completed Lysholm responses. A per-protocol analysis (including only those participants who received their randomized allocation) was carried out as supportive analysis on the primary outcomes. The number of participants experiencing an additional procedure or SAE was analyzed using a chi-square test. Point estimates and 95% CIs are presented for the joint primary outcome measures; a Bonferroni correction was applied to the 2-sided P value to allow conventional interpretation at the 5% level. Other outcomes were presented with 99% CIs. SAS Version 9.4 (SAS Institute) was used for analysis.

RESULTS

Patients and Follow-up

In total, 390 patients from 27 UK centers and 2 centers in Norway were randomized between December 2004 and January 2011 (Figure 1). Baseline characteristics of the participants in both groups were similar (Table 1). The mean (SD) age was 35 (9) years (range, 16-56 years), and 64% were male (251/390). The most common previous procedure in both groups was debridement (34% and 41% in the ACI and best alternative group, respectively). In terms of previous cartilage repair, in the ACI group, 112/195 (57%) had undergone no previous cartilage surgery involving marrow stimulation, 57 (29%) had undergone marrow stimulation, and 3 (2%) had undergone previous ACI. In the standard group, 114/195 (58%) had undergone no previous cartilage surgery involving marrow stimulation, 67 (34%) had undergone previous marrow stimulation, and 1 (1%) had undergone previous ACI. Most defects—88% (342/390)—were femoral, with a mean (SD) of 3.2 (2.1) cm^2 in size. The median duration of symptoms was 3 years (interquartile range [IQR], 2-5). Follow-up from participants in the form of a completed patient Lysholm was 76% (296/390) at 5 years, although 93% (362/390) provided $\geq$1 response within 5 years and contributed to analysis of this outcome.

Treatment

Despite some switching after randomization from intended standard treatment type to another standard treatment (eg, microfracture to debridement) and within variations of ACI technique (eg, periosteum to collagen patch), 89%

TABLE 1
Participant Characteristics at Baseline[a]

Baseline Data	ACI (n = 195)	Standard (n = 195)
Type of previous procedure		
Debridement	67 (34)	80 (41)
Microfracture	46 (24)	53 (27)
Washout	28 (14)	23 (12)
Arthroscopy	17 (9)	11 (6)
Drilling	10 (5)	12 (6)
Mosaicplasty	2 (1)	2 (1)
Abrasion	1 (1)	2 (1)
ACI (collagen)	1 (1)	1 (1)
Chondron	1 (1)	0 (0)
AMIC	1 (1)	0 (0)
Other	21 (11)	11 (6)
Type of previous procedure[b]		
Previous marrow stimulation	57 (29)	67 (34)
No previous marrow stimulation	138 (71)	128 (66)
Intended standard arm[c]		
Microfracture	97 (50)	95 (49)
AMIC	54 (28)	55 (28)
Mosaicplasty	21 (11)	20 (10)
Debridement	13 (7)	13 (7)
Bone graft	9 (5)	10 (5)
Drilling	1 (1)	2 (1)
Intended ACI arm		
ACI subrandomised (collagen/periosteum)	99 (51)	99 (51)
MACI	55 (28)	56 (29)
ACI (collagen)	31 (16)	28 (14)
ACI subrand (MACI/Chondron)	9 (5)	10 (5)
ACI (periosteum)	1 (1)	2 (1)
Size of chondral defect,[c] cm^2		
<2.0	48 (25)	45 (23)
2.0-3.9	70 (36)	76 (39)
4.0-7.9	67 (34)	66 (34)
8.0 +	10 (5)	8 (4)
Mean (SD)	3.2 (2.1)	3.2 (2.0)
Age group, years[c]		
0-29	52 (27)	51 (26)
30-39	76 (39)	76 (39)
40-49	57 (29)	57 (29)
50 +	10 (5)	11 (6)
Mean (SD)	35.4 (9.2)	35.4 (8.9)
Preoperative Lysholm score[c]		
0-49	98 (50)	98 (50)
50-64	59 (30)	58 (30)
65-83	32 (16)	32 (16)
84 +	6 (3)	7 (4)
Mean (SD)	48.6 (18.5)	48.8 (17.8)
Type of defect[c]		
Femoral	171 (88)	171 (88)
Trochlear/patella	24 (12)	24 (12)
Affected knee		
Left	91 (47)	95 (49)
Right	104 (53)	100 (51)
Sex		
Male	125 (64)	126 (65)
Female	70 (36)	69 (35)
Symptom duration		
<3 years	68 (35)	77 (39)
≥3 years	118 (60)	101 (52)
Median (IQR)	3.4 (2.0-5.5)	3.0 (2.0-5.0)
Missing	9 (5)	17 (9)
Time to surgery, median (IQR), d	64 (45-94)	29 (16-60)
Time since previous surgery, median (IQR), y	1.5 (1.1-2.2)	1.3 (0.9-2.4)

[a]Values are presented as No. (%) unless otherwise indicated. ACI, autologous chondrocyte implantation; AMIC, autologous matrix induced chondrogenesis; IQR, interquartile range; MACI, Matrix-induced Autologous Chondrocyte Implantation.
[b]Previous marrow stimulation=microfracture, drilling or abrasion
[c]Minimization variable used in randomisation procedure

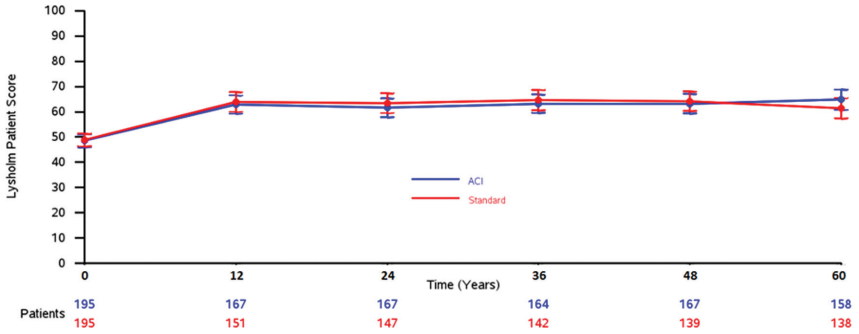

Figure 2. Joint primary outcome—evolution over time of Lysholm patient-completed scores. ACI, autologous chondrocyte implantation.

(174/195) of participants allocated ACI received an ACI technique. The corresponding figure in the standard arm was 86% (168/195). Fourteen participants crossed over from ACI to standard treatment, 5 vice versa, and 22 did not receive any surgery after randomization (see the Appendix, available in the online version of this article). Microfracture was selected as the most popular standard comparator (192/390; 49%) and, together with AMIC, formed approximately four-fifths (301/390) of the standard intended surgery types. The median time from onset of symptoms to surgery in the ACI group was 3.4 years (IQR, 2.0-5.5) versus 3.0 years (IQR, 2.0-5.0) in the standard group.

Joint Primary Outcome—Lysholm Scores (Patient Completed)

Overall, scores were improved by 1 year in both groups (15.4 points, 95% CI, 11.9-18.8 with ACI; 15.2 points, 95% CI, 11.6-18.9 with standard treatment) (Table 2), with this improvement was sustained over 5 years (Figure 2). Some evidence of time × treatment interaction was noted (P = .04), so treatment effect estimates were examined at each time point. For the overall group, scores were slightly higher at 5 years in the ACI group (2.9 points; 95% CI, −1.8 to 7.5), but this difference was not statistically significant (P = .46). There was no evidence of any difference in treatment effect between groups at the other time points. Sensitivity analyses did not materially change the results (see the Appendix, available in the online version of this article). There was evidence of a differential effect (P = .03) in favor of ACI in patients without a history of marrow stimulation compared with those who had undergone previous stimulation (6.4-point difference in favor of ACI; 95% CI, −0.4 to 13.1). Further subgroup analysis identified no association between outcome and age, lesion size, duration of symptoms, preoperative Lysholm score, or defect location (Figure 3). A per-protocol analysis on the joint primary outcomes demonstrated similar outcomes, with no significant differences between groups (see the Appendix, available in the online version of this article).

Joint Primary Outcome—Time to Cessation of Benefit

By 5 years after operation, just over half of participants in both groups were still experiencing benefit from surgery (55% with ACI, 95% CI, 47%-64%; 54% with best alternative treatment, 95% CI, 47%-62%), with no evidence of difference between groups (hazard ratio [HR], 0.97; 95% CI, 0.72-1.32; p-value>0.99) (Figure 4). Sensitivity analysis did not alter the interpretation. Where scheduled assessments were completed, 69 of 144 (48%) failed on all 3 outcome components, with the remainder failing on a mixture of 2 of 3 independent and patient-reported components. Most failures materialized at 1 and 3 years because of assessments primarily completed at these times. Per-protocol analyses returned similar results to the intention-to-treat analyses (see the Appendix, available in the online version of this article).

Secondary Outcomes and Safety

There were no consistent effects in the secondary outcomes over the full period of follow-up. The IKDC score in the ACI group was statistically superior to the standard group at 4 years (P = .05) and 5 years (P = .02) after surgery (Table 2). SAEs were observed in 33 (17%) of participants in the ACI group and 17 (9%) of participants in the standard treatment group (P = .02). Of these, 16 (8%) versus 5 (3%), respectively, were judged to be treatment-related. The commonest treatment-related adverse event reported in both groups was knee pain. Two patients in the ACI group had graft hypertrophy; both patients had received ACI-P. There was 1 treatment-related Deep Vein Thrombosis (DVT) in the ACI group.

DISCUSSION

The results of this trial show that both ACI and best alternative treatments improve knee function as measured using the Lysholm patient-reported knee score, the IKDC, and Cincinnati score. The increase in score of

TABLE 2
Results of Patient- and Assessor-Completed Questionnaires[a]

Time Point	ACI	Standard	Adjusted Mean Difference (CI)[b] [*P* Value]
Joint primary outcome—Lysholm patient-completed scores[c]			
Prerandomization	n = 195	n = 195	—
	48.58 [18.46]	48.83 [17.83]	
1 year	n = 167	n = 151	−1.9 (−6.3 to 2.4) [.38]
	62.88 [23.50]	63.95 [24.27]	
2 years	n = 167	n = 147	−0.7 (−4.7 to 3.2) [.71]
	61.60 [24.31]	63.46 [23.95]	
3 years	n = 164	n = 142	0.5 (−3.4 to 4.3) [.82]
	63.18 [23.47]	64.65 [24.47]	
4 years	n = 167	n = 139	1.7 (−2.5 to 5.8) [.43]
	63.23 [25.39]	64.23 [22.97]	
5 years	n = 158	n = 138	2.9 (−1.8 to 7.5) [.46]
	64.78 [25.53]	61.48 [23.82]	
Secondary outcome—Lysholm assessor-completed scores[d]			
Prerandomization	n = 189	n = 186	0.8 (−4.7 to 6.4) [.70]
	50.61 [20.14]	51.24 [20.24]	
1 year	n = 149	n = 126	
	69.38 [23.20]	68.64 [24.07]	
3 years	n = 139	n = 122	
	66.15 [24.78]	68.59 [25.57]	
5 years	n = 118	n = 95	
	72.75 [23.18]	68.64 [25.17]	
Secondary outcome (patient completed)—IKDC knee rating scores[e]			
Prerandomization	n = 189	n = 185	—
	39.1 [15.0]	40.9 [15.0]	
1 year	n = 165	n = 148	0.17 (−5.28 to 5.63) [.93]
	53.9 [22.5]	54.0 [23.4]	
2 years	n = 165	n = 144	1.48 (−3.59 to 6.54) [.45]
	54.6 [23.0]	54.8 [24.0]	
3 years	n = 162	n = 138	2.79 (−2.28 to 7.86) [.16]
	54.9 [23.2]	56.5 [25.2]	
4 years	n = 148	n = 130	4.09 (−1.37 to 9.56) [.05]
	56.8 [24.9]	53.8 [23.6]	
5 years	n = 139	n = 121	5.40 (−0.78 to 11.58) [.02]
	57.3 [24.9]	53.8 [23.5]	
Secondary outcome (patient completed)—EQ-5D-3L EuroQol score[f]			
Prerandomization	n = 192	n = 187	0.01 (−0.05 to 0.07) [.59]
	0.51 [0.28]	0.53 [0.29]	
1 year	n = 168	n = 150	
	0.64 [0.31]	0.67 [0.28]	
2 years	n = 165	n = 147	
	0.67 [0.29]	0.67 [0.30]	
3 years	n = 164	n = 140	
	0.67 [0.29]	0.67 [0.30]	
4 years	n = 151	n = 135	
	0.66 [0.31]	0.68 [0.30]	
5 years	n = 140	n = 124	
	0.67 [0.33]	0.64 [0.30]	
Secondary outcome (patient completed)—EQ-5D-3L Health score[g]			
Prerandomization	n = 193	n = 187	−1.06 (−5.49 to 3.36) [.53]
	65.66 [19.24]	64.05 [20.91]	
1 year	n = 168	n = 150	
	69.98 [20.66]	70.97 [20.33]	
2 years	n = 167	n = 147	
	70.08 [20.92]	71.19 [20.82]	
3 years	n = 164	n = 140	
	72.29 [21.88]	69.70 [22.58]	
4 years	n = 151	n = 135	
	71.44 [22.84]	72.21 [19.43]	
5 years	n = 140	n = 124	
	70.57 [21.97]	71.02 [19.88]	

[a]ACI, autologous chondrocyte implantation; EQ-5D-3L, EuroQol 5 Dimensions; IKDC, International Knee Documentation Committee.

[b]Effect size is the adjusted mean difference and the confidence intervals are 99% for all secondary outcomes and 95% for the joint-primary outcome. Estimates at each time-point only considered if the overall treatment by time interaction term was <0.05. Analysis models were adjusted for the baseline score for each outcome (where available).

[c]Time by treatment interaction: p = 0.04 so estimates produced at each time point; min = 0, max = 100, difference>0 favour ACI

[d]Time by treatment interaction: p = 0.41 so constant treatment effect assumed; min = 0, max = 100, difference>0 favour ACI

[e]Time by treatment interaction: p = 0.02 so estimates produced at each time point; min = 0, max = 100, difference>0 favour ACI

[f]Time by treatment interaction: p = 0.23 so constant treatment effect assumed; min = –0.59, max = 1, difference>0 favour ACI

[g]Time by treatment interaction: p = 0.45 so constant treatment effect assumed; min = 0, max = 100, difference>0 favour ACI

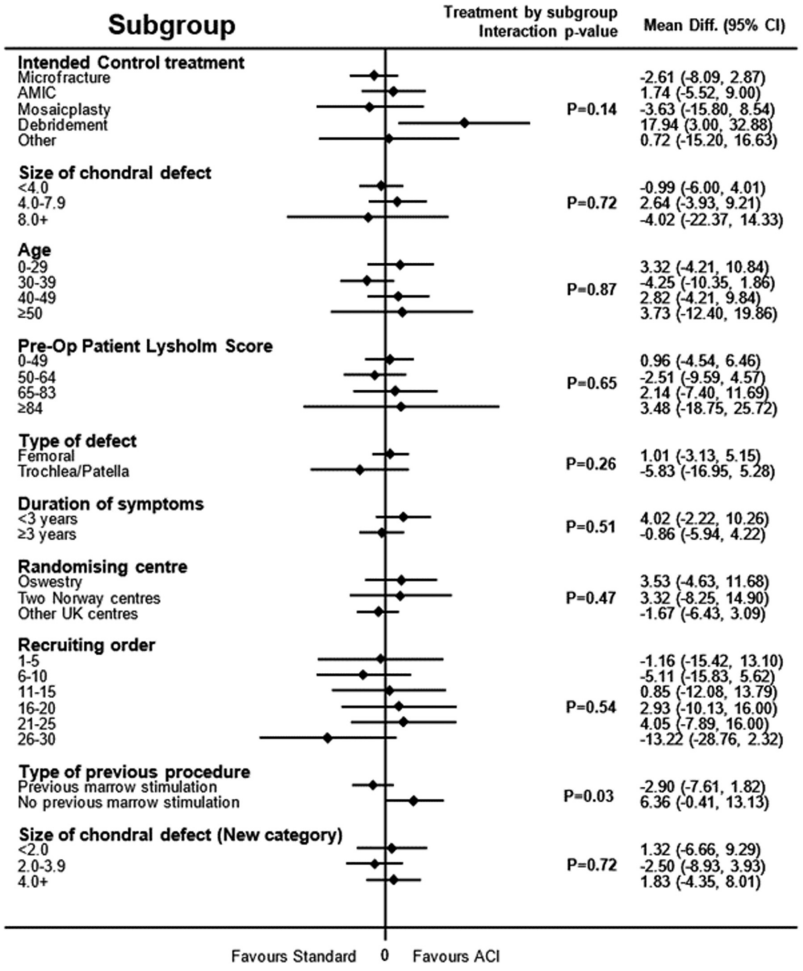

Figure 3. Planned subgroup analysis—Lysholm patient-completed scores. AMIC, Autologous matrix-induced chondrogenesis; Pre-Op, preoperative.

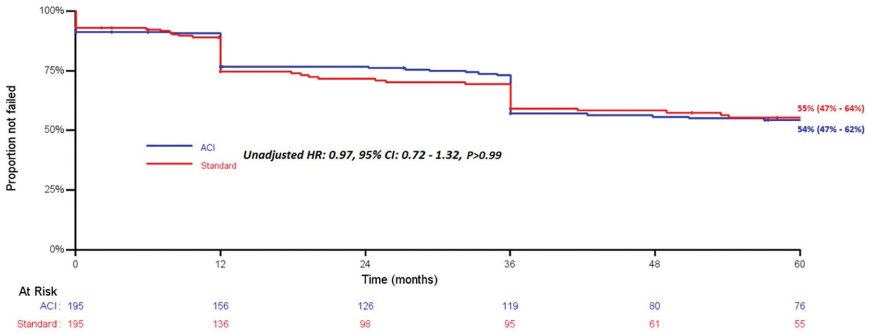

Figure 4. Joint primary outcome—time to cessation of treatment benefit. A Cox proportional hazards model was fitted; values <1 favor autologous chondrocyte implantation (ACI) arm. HR, hazard ratio.

approximately 15 points on the Lysholm scale in both groups represented an effect size of approximately two-thirds of a standard deviation, and hence is likely to be clinically meaningful.[29] The increase is greater than the range for the minimal clinically important difference (MCID) of 4.3 to 10.5 reported by Ogura et al.[32] Similarly, the mean increase of approximately 16 points on the IKDC scale is within the upper range of the MCID for the IKDC (10.8-16.4). Lysholm knee scores improved marginally more after ACI compared with alternative surgery, but the difference was not statistically convincing. Treatment benefit, assessed through a combination of assessor and

patient assessments, was sustained for approximately half of patients in each treatment arm at 5 years after surgery.

The potential therapeutic benefit of ACI over other forms of cartilage repair is anticipated to be in the mid to long term (>5 years) given that remodeling and maturation of the cartilage repair tissue occur over years.[34,37] Conversely, there is accumulating evidence that the failure rate after marrow stimulation increases over the midterm,[14] with deteriorating outcomes out to 10 years and radiographic progression of osteoarthritis after 5 years.[13] A recent meta-analysis of randomized controlled trials involving 659 patients found no significant difference in the improvement of IKDC and Lysholm scores or overall Knee Injury and Osteoarthritis Outcome Score (KOOS) measures between patients in ACI and microfracture groups at 1-year, 2-year, and 5-year follow-up examinations or in failure rate at 2-year, 3-year, and 5-year follow-up time points.[9] However, patients treated with ACI had a significant benefit in activities of daily living. ACI also showed better improvement in quality of life and pain relief than microfracture at 5-year and 2-year follow-up examinations, respectively.[10] A similar analysis of only modified versions of ACI (ACI-C or MACI) also found significantly more improvement compared with microfracture in clinical outcomes after 5 years as determined by KOOS, activities of daily living assessment, Tegner Activity Scale score, and the IKDC objective and subjective scores.[26]

The length of the present study and its pragmatic nature meant that the ACI product used by the treating centers varied and was dictated by availability. The lead center manufactured its own chondrocytes and initially used first-generation ACI-P before switching to a second-generation technique with a collagen membrane. Most of the other recruiting sites used MACI (as the only commercial product available), with 1 site also having access to a second commercial product, Chondron. ACI-P contributed 26% of the ACI performed in this study, which has been shown to be inferior to second-generation ACI-C.[28] Conversely, in the standard group, the overall results were potentially improved given that 28% of patients received AMIC, which has been shown to provide superior results to microfracture alone.[12,20] These 2 factors may have consequently had an effect on the 5-year outcomes in our trial. It is anticipated that the 10-year results will prove to be more informative as to the true therapeutic effects of the various treatments. No direct comparisons between the different methods of ACI or between standard treatments were undertaken. ACTIVE was designed as a pragmatic trial, and surgeons were encouraged to use the treatment that they were most comfortable with. Any potential comparisons between modalities of ACI or standard treatments would be nonrandomized and subject to confounding; hence, we believe they would have limited value.

The increased failure of marrow stimulation beyond the midterm is thought to be largely secondary to its detrimental effects on the bone. Subchondral abrasion, drilling, and microfracture all stimulate a callus response, resulting in the formation of fibrous tissue and subchondral bone changes, which lead to the eventual return of clinical symptoms.[14,21,23,24] Violation of the tidemark and subchondral bone commonly leads to progression from a flush bone plate to subchondral bone elevation and intralesional osteophyte, which have been observed more in microfracture compared with ACI patients 36 months after surgery.[36] A sheep model has demonstrated that compared with untreated defects, treating a chondral defect with microfracture or AMIC led to subchondral bone changes, in particular an increased bone volume fraction, increased trabecular thickness, and decreased trabecular separation, which extended beyond the area below the defect.[2] These changes alter the biomechanical properties of the subchondral bone plate and therefore limit tissue repair durability. Subchondral bone elevation decreases cartilage volume and gives rise to biomechanical overloading and peak stresses. The effect of the subchondral bone changes extends beyond the failure of the primary repair and likely influences the outcome of any future chondral procedure.

In all, 32% of ACTIVE participants had previous marrow stimulation, 29% in the ACI group and 34% in the standard group. ACTIVE therefore enables investigation into the influence of previous cartilage repair surgery as part of a randomized controlled trial, rather than an observational cohort study. In the ACI group, there was an apparent detrimental effect on the Lysholm score in patients with a history of marrow stimulation (6.4 points; 95% CI, −0.4 to 13.1; test for interaction $P = .03$). The effects of previous marrow stimulation on cessation of benefit and the secondary end points were not analyzed as part of the 5-year report (as this effect was not anticipated in the statistical analysis plan devised before commencement of the study in early 2000s), but these data will inform the 10-year analysis plan. This negative effect of previous marrow stimulation correlates with the findings of others.[21,25,27,33] Minas et al[21] compared 2 matched cohorts of patients who had ACI-P, one group (111 patients) having had previous marrow stimulation procedures (microfracture, drilling, or abrasion arthroplasty) and the other (214) not. The failure rate in those who had ACI as the first procedure was 8% (17/214) but was 26% (29/111) in those who had had previous marrow procedures. Nawaz et al[27] reported the results of 1000 patients after ACI between 1998 and 2008. In 827 patients with full follow-up data (mean follow-up, 6.2 years), graft survival was 78% at 5 years and 51% at 10 years. Failure of the graft was 4.7 times more likely in the 34% who had had previous procedures. The survival rate in ACTIVE is lower, despite a similar percentage of patients with previous marrow stimulation. However, the definition of failure in ACTIVE was stricter and based more on patient-reported and assessor outcomes. In addition, there is the potential for surgeon bias as the procedures in the Nawaz et al[27] study were undertaken in a single high-volume center by a small number of surgeons as compared with the 29 centers in this study, with the majority undertaking much lower volumes annually. Of note was that no detrimental effect of previous microfracture was observed in the standard group, despite nearly 80% of patients in that group undergoing a further marrow stimulation procedure. The

increasing evidence demonstrating a clear negative effect of marrow stimulation on the outcomes of secondary ACI highlights the importance of primary decision-making when treating patients with cartilage lesions. Patients can be considered for ACI as a revision procedure after marrow stimulation, but they need to be appropriately counseled with regard to a higher failure rate.

There were significantly more SAEs in the ACI group compared with the standard group, both overall (17% vs 9%) and treatment-related (8% vs 3%). It is to be expected that the number of adverse events would be greater in the ACI group, given the need for 2 surgeries and the more invasive nature of the treatment. The overall treatment-related adverse events are comparative with those reported in the SUMMIT (15.3%)[35] and TIG/ACT (4%) trials,[36] 2 other RCTs comparing ACI versus microfracture.

ACTIVE is the largest randomized comparison involving ACI to date. We recruited from a large number of centers across the United Kingdom and Norway, and the trial design allowed variations in comparator treatments that were thought to be the most appropriate by each recruiting surgeon. These elements allow for increased generalizability of the findings.[9] Good levels of follow-up were attained, with 93% of participants able to contribute to the analysis of functional knee score responses. Outcome assessment was comprehensive, using a mixture of functional and quality-of-life questionnaires. The inclusion of repeat assessments using an assessor blinded to the treatment allocation added to this rigorous appraisal of outcomes after surgery. The study protocol was devised in the early 2000s under the practical and financial constraints of using ACI within a public health system. Consequently, there are a number of weaknesses. The outcome measures used were the most appropriate at the time and were consistent with other cartilage trials of the period.[3] The study predates the validation of more modern-day scores such as the KOOS. The primary outcome of interest was a clinical and functional outcome measure with no availability of funds to undertake posttreatment magnetic resonance imaging (MRI) or histologic assessment on a large scale. Over the 20 years since the creation of the study protocol, the increasing importance of alignment and meniscal function on the outcome of cartilage repair has been highlighted.[15] The inclusion criteria of modern-day trials are consequently stricter and centrally confirmed, in terms of allowed mechanical axis deviation (<5 degrees)[37] and restriction of meniscal loss to <50%.[35] It is likely that the pragmatic nature of our study led to the inclusion of patients who would be excluded if the trial was commenced now, and this has likely affected the overall results in both groups.

The study was originally powered to detect a 30% relative difference in cessation of benefit of treatment. Unfortunately, we were not able to reach the required sample size, stopping some 270 participants short because of difficulty with recruitment. Inherent to cartilage trials, the need to exclude patients requiring associated procedures limits the number of eligible patients, which can lead to recruitment delays. This size of sample would have 67% power to detect the size of difference originally planned in cessation of benefit. However, ACTIVE had high power (90%) to detect small to moderate differences (0.34 SD) in Lysholm score (retrospective calculation). Of those randomized, 48 (12%) did not receive their allocated intervention, with a number of those randomized to ACI ultimately considered unsuitable for this treatment at the time of planned harvest biopsy. This was in the main the result of a disparity between the arthroscopic findings and the preoperative MRI. The effect of this was explored through sensitivity analyses, including only those who received the correct allocation, but this did not materially alter the results. Similarly, per-protocol analyses demonstrated no significant differences between groups in terms of Lysholm score or cessation of benefit.

The results from ACTIVE at the initial 5-year assessment failed to demonstrate a significant difference in either of the primary outcome measures between ACI and best alternative standard treatment in patients who have failed previous surgery. The study was ultimately underpowered to detect a difference in cessation of benefit but was highly powered to detect small to moderate differences in Lysholm score. There was evidence to suggest a greater improvement in IKDC in the ACI group and that previous marrow stimulation had a detrimental effect on the outcome of ACI at 5 years. Given the expected patterns of outcomes for the various forms of cartilage repair included in this trial, it is anticipated that the 10-year outcomes of the study will provide a better indication of any superior therapeutic benefit.

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REFERENCES

1. Bailey A, Goodstone N, Roberts S, et al. Rehabilitation after Oswestry autologous-chondrocyte implantation: the OsCell protocol. *J Sport Rehabil*. 2003;12(2):104-118.
2. Beck A, Murphy DJ, Carey-Smith R, Wood DJ, Zheng MH. Treatment of articular cartilage defects with microfracture and autologous matrix-induced chondrogenesis leads to extensive subchondral bone cyst formation in a sheep model. *Am J Sports Med*. 2016;44(10):2629-2643.
3. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. *N Engl J Med*. 1994;331(14):889-895.
4. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. *Instr Course Lect*. 1998;47:487-504.
5. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Academic Press; 1977.
6. EuroQol Group. EuorQol EQ-5D. https://euroqol.org (accessed January 3, 2023)
7. Farr J, Cole B, Dhawan A, Kercher J, Sherman S. Clinical cartilage restoration: evolution and overview. *Clin Orthop Relat Res*. 2011;469(10):2696-2705.
8. Fitzmaurice G, Laird N, Ware J. *Applied Longitudinal Analysis*. 2nd ed. Wiley; 2011.
9. Gou GH, Tseng FJ, Wang SH, et al. Autologous chondrocyte implantation versus microfracture in the knee: a meta-analysis and systematic review. *Arthroscopy*. 2020;36(1):289-303.
10. Hinckel BB, Gomoll AH. Patellofemoral cartilage restoration: indications, techniques, and outcomes of autologous chondrocytes implantation, matrix-induced chondrocyte implantation, and particulated juvenile allograft cartilage. *J Knee Surg*. 2018;31(3):212-226.
11. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the International Knee Documentation Committee Subjective Knee Form. *Am J Sports Med*. 2001;29(5):600-613.
12. Kim JH, Heo JW, Lee DH. Clinical and radiological outcomes after autologous matrix-induced chondrogenesis versus microfracture of the knee: a systematic review and meta-analysis with a minimum 2-year follow-up. *Orthop J Sports Med*. 2020;8(11):232596712095928.
13. Kim JK, Vaidya R, Lee SK, et al. Clinical and radiological changes after microfracture of knee chondral lesions in middle-aged Asian patients. *Clin Orthop Surg*. 2019;11(3):282.
14. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. *Osteoarthritis Cartilage*. 2006;14(11):1119-1125.
15. Krych AJ, Hevesi M, Desai VS, Camp CL, Stuart MJ, Saris DBF. Learning from failure in cartilage repair surgery: an analysis of the mode of failure of primary procedures in consecutive cases at a tertiary referral center. *Orthop J Sports Med*. 2018;6(5):2325967 11877304.
16. Lysholm J, Gillquist J. Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med*. 1982;10:150-154.
17. Marijnissen ACA, Lafeber FPJG. Re: E. B. Hunziker. Articular cartilage repair: basic science and clinical progress. A review of the current status and prospects. Osteoarthritis and Cartilage 2002; 10:432-63. *Osteoarthritis Cartilage*. 2003;11(4):300-301.
18. Marlovits S, Striessnig G, Resinger CT, et al. Definition of pertinent parameters for the evaluation of articular cartilage repair tissue with high-resolution magnetic resonance imaging. *Eur J Radiol*. 2004;52(3):310-319.
19. Medical Services Advisory Committee (MSAC). Matrix-induced autologous chondrocyte implantation (MACI) and autologous chondrocyte

implantation (ACI). 2010. www.msac.gov. au/internet/msac/publishing.nsf/Content/1140–public (accessed January 3, 2023)
20. Migliorini F, Eschweiler J, Maffulli N, et al. Autologous matrix-induced chondrogenesis (AMIC) and microfractures for focal chondral defects of the knee: a medium-term comparative study. *Life*. 2021;11(3):183.
21. Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med*. 2009;37(5):902-908.
22. Mistry H, Connock M, Pink J, et al. Autologous chondrocyte implantation in the knee: systematic review and economic evaluation. *Health Technol Assess*. 2017;21(6). doi:10.3310/hta21060.
23. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. *Am J Sports Med*. 2009;37(10):2053-2063.
24. Mithoefer K, Williams RJ, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee: a prospective cohort study. *J Bone Joint Surg Am*. 2005;87(9):1911-1920.
25. Müller PE, Gallik D, Hammerschmid F, et al. Third-generation autologous chondrocyte implantation after failed bone marrow stimulation leads to inferior clinical results. *Knee Surg Sports Traumatol Arthrosc*. 2020;28(2):470-477.
26. Na Y, Shi Y, Liu W, et al. Is implantation of autologous chondrocytes superior to microfracture for articular-cartilage defects of the knee? A systematic review of 5-year follow-up data. *Int J Surg*. 2019;68:56-62.
27. Nawaz S, Bentley G, Briggs TWR, et al. Autologous chondrocyte implantation in the knee: mid-term to long-term results. *J Bone Joint Surg Am*. 2014;96:824-830.
28. Niemeyer P, Salzmann G, Feucht M, et al. First-generation versus second-generation autologous chondrocyte implantation for treatment of cartilage defects of the knee: a matched-pair analysis on long-term clinical outcome. *Int Orthop*. 2014;38(10):2065-2070.
29. Norman G, Sloan J, Wyrwich K. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care*. 2003;41(5):582-592.
30. Noyes F, Matthews D, Mooar P, Grood E. The symptomatic anterior cruciate-deficient knee. Part II: the results of rehabilitation, activity modification, and counselling on functional disability. *J Bone Joint Surg Am*. 1983;65(2):163-174.
31. Noyes FR, Mooar P, Matthews D, Butler D. The symptomatic anterior cruciate-deficient knee. Part I: the long-term functional disability in athletically active individuals. *J Bone Joint Surg Am*. 1983;65(2): 154-162.
32. Ogura T, Ackermann J, Barbieri Mestriner A, Merkely G, Gomoll AH. Minimal clinically important differences and substantial clinical benefit in patient-reported outcome measures after autologous chondrocyte implantation. *Cartilage*. 2020;11(4):412-422.
33. Pestka JM, Bode G, Salzmann G, Südkamp NP, Niemeyer P. Clinical outcome of autologous chondrocyte implantation for failed microfracture treatment of full-thickness cartilage defects of the knee joint. *Am J Sports Med*. 2012;40(2):325-331.
34. Roberts S, Hollander A, Caterson B, Menage J, Richardson J. Matrix turnover in human cartilage repair tissue in autologous chondrocyte implantation. *Arthritis Rheum*. 2001;44(11):2586-2598.
35. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: two-year follow-up of a prospective randomized trial. *Am J Sports Med*. 2014;42(6):1384-1394.
36. Saris DBF, Vanlauwe J, Victor J, et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. *Am J Sports Med*. 2009;37(1) (suppl):10-19.
37. Vanlauwe J, Saris DBF, Victor J, et al; TIG/ACT/01/2000&EXT Study Group. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. *Am J Sports Med*. 2011; 39(12):2566-2574.
38. Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data*. Springer; 2000.
39. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. *Knee*. 2007;14(3):177-182.