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Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture

Two-Year Follow-up of a Prospective Randomized Trial

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Investigation performed at several sites sponsored by Sanofi

Background: Randomized controlled trials studying the efficacy and safety of matrix-applied characterized autologous cultured chondrocytes (MACI) versus microfracture (MFX) for treating cartilage defects are limited.

Purpose: To compare the clinical efficacy and safety of MACI versus MFX in the treatment of patients with symptomatic cartilage defects of the knee.

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

Methods: Patients enrolled in the SUMMIT (Demonstrate the Superiority of MACI implant to Microfracture Treatment) trial had $\geq$1 symptomatic focal cartilage defect (Outerbridge grade III or IV; $\geq$3 cm^2) of the femoral condyles or trochlea, with a baseline Knee Injury and Osteoarthritis Outcome Score (KOOS) pain value <55. The co–primary efficacy endpoint was the change in the KOOS pain and function subscores from baseline to 2 years. Histological evaluation and magnetic resonance imaging (MRI) assessments of structural repair tissue, treatment failure, the remaining 3 KOOS subscales, and safety were also assessed.

Results: Of the 144 patients treated, 137 (95%) completed the 2-year assessment. Patients had a mean age of 33.8 years and a mean lesion size of 4.8 cm^2. The mean KOOS pain and function subscores from baseline to 2 years were significantly more improved with MACI than with MFX (pain: MACI, 37.0 to 82.5 vs MFX, 35.5 to 70.9; function: MACI, 14.9 to 60.9 vs MFX, 12.6 to 48.7; P = .001). A significant improvement in scores was also observed on the KOOS subscales of activities of daily living (MACI, 43.5 to 87.2 vs MFX, 42.6 to 75.8; $P < .001$), knee-related quality of life (MACI, 18.8 to 56.2 vs MFX, 17.2 to 47.3; P = .029), and other symptoms (MACI, 48.3 to 83.7 vs MFX, 44.4 to 72.2; $P < .001$) for patients treated with MACI compared with MFX. Repair tissue quality was good as assessed by histology/MRI, but no difference was shown between treatments. A low number of treatment failures (nonresponders: MACI, 12.5% vs MFX, 31.9%; P = .016) and no unexpected safety findings were reported.

Conclusion: The treatment of symptomatic cartilage knee defects $\geq$3 cm^2 in size using MACI was clinically and statistically significantly better than with MFX, with similar structural repair tissue and safety, in this heterogeneous patient population. Moreover, MACI offers a more efficacious alternative than MFX with a similar safety profile for the treatment of symptomatic articular cartilage defects of the knee.

Keywords: cartilage repair; clinical outcomes; knee; matrix-applied characterized autologous cultured chondrocytes (MACI) implant; microfracture

Cell therapy has been an integral part of the technovolution[20] in cartilage repair, utilizing autologous chondrocytes to generate effective repair tissue. Treating cartilage lesions is important as cartilage injuries are prevalent and can lead to significant pain and reduced function.[39] If left untreated, cartilage lesions can become symptomatic and may progress to osteoarthritis.[38]

The first autologous chondrocyte implantation (ACI) procedure for cartilage repair was performed 25 years ago.[4] Over time, the procedure has advanced to collagen-covered ACI (second-generation technology)[13] and then to matrix-applied characterized autologous cultured chondrocytes (MACI; Genzyme Biosurgery, Cambridge, Massachusetts, USA) implantation, which is third-generation technology. Progression to third-generation technology

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resulted in added benefits to patients including shorter procedure time, better surgical consistency, a smaller incision, more consistent cell seeding, less periosteal hypertrophy, and fewer adverse events.[3,7,18,31] For MACI, cultured chondrocytes are seeded in a collagen membrane, which is implanted in the defect. Culturing cells in the membrane allows for their redifferentiation to a more chondrogenic phenotype after monolayer culture; cells are better fixed and distributed in the defect.[3,10,11,40] Physical properties of the type I/III collagen membrane (ACI-Maix, Matricel GmbH, Herzogenrath, Germany) make it tear resistant and durable and thus permit the implant to be easily trimmed and handled.[3,10,11] Overall, good clinical outcomes and repair tissue have been shown with MACI with a good safety profile and especially less periosteal hypertrophy than with the ACI procedure.[3,6,7,18]

Microfracture (MFX), a bone marrow stimulating procedure,[34] is frequently used to repair specific cartilage injuries. While MFX provides good clinical outcomes, these are not always sustained.[15,16,23,25] Previous studies show that patients with smaller lesions have better clinical outcomes with MFX than patients with larger lesions,[21] whereas lesions on the trochlea do not improve as well as those on the femoral condyle.[16] Repair tissue with MFX has been shown to be fibrous in nature[30] compared with more hyaline-like repair tissue reported with MACI.[3] In addition, intralesional osteophytes may result from MFX and could compromise any successful clinical outcomes with the procedure.[22] Also, MFX may negatively affect outcomes of subsequent cell-based cartilage repair treatment.[22,27]

We have conducted the largest randomized controlled trial with the highest power to date in cartilage repair, consistent with the guidance of regulatory agencies, comparing MACI with MFX. Although MFX is traditionally used for the treatment of smaller lesions, clinicians also treat larger defects with MFX[23] because there are few established or acceptable alternative treatment options. The primary objective of our study was to compare the clinical efficacy and safety of MACI with MFX in the treatment of patients with symptomatic knee cartilage defects $\geq$3 cm^2 in size.

MATERIALS AND METHODS

Study Design

The SUMMIT (Demonstrate the Superiority of MACI implant to Microfracture Treatment) trial (in patients with symptomatic articular cartilage defects in the knee) was a prospective, randomized, open-label, parallel-group, multicenter study conducted at 16 European sites (NCT00719576), with enrollment beginning in May 2008. Cartilage defects of the medial femoral condyle (MFC), lateral femoral condyle (LFC), and/or trochlea were treated with MACI or arthroscopic MFX. The protocol and informed consent form were approved by the appropriate national/local ethics committee at each site. The study was conducted according to Good Clinical Practice (GCP) guidelines and principles of the Declaration of Helsinki. All patients provided written informed consent before participating. All surgeons were trained on all surgical procedures, which were standardized.

Patient Population

Male and female patients aged 18 to 55 years with $\geq$1 symptomatic cartilage defects and a moderate to severe Knee Injury and Osteoarthritis Outcome Score (KOOS) pain value (<55) at baseline were included. Index defects

Note: MACI was recently registered as the name of the medicinal product (matrix applied characterised autologous cultured chondrocytes) licensed for cartilage cell therapy use in Europe and manufactured by Sanofi Biosurgery (formerly Genzyme Biosurgery).

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were Outerbridge grade III or IV focal cartilage defects[26] on the MFC, LFC, and/or trochlea and were $\geq$3 cm^2 in size. Osteochondritis dissecans (OCD) lesions were allowed if no bone graft was required. A stable knee was required; ligament reconstruction procedures were allowed before or concurrently with the study treatment. An intact or partial meniscus ($\geq$50%) was also required; meniscal repair or resection was allowed before or concurrently with the cartilage repair procedure if $\geq$50% of the functional meniscus remained.

Major exclusion criteria included any knee joint surgery within 6 months before screening; modified Outerbridge grade III or IV defect(s)[26] on the patella or tibia; a symptomatic musculoskeletal condition in the lower limbs that could impede efficacy measures in the target knee; total meniscectomy, meniscal allograft, or bucket-handle tear or displaced tear requiring >50% removal of the meniscus in the target knee; malalignment requiring osteotomy to correct tibial-femoral or patella-femoral alignment; Kellgren-Lawrence grade 3 or 4 osteoarthritis; inflammatory disease or other condition affecting the joints; or septic arthritis within 1 year before screening.

Surgical Procedures

The control selected for efficacy comparison was MFX as recommended by the United States Food and Drug Administration (FDA) and European Medicines Agengy (EMA) in their guidances.[9,35] Microfracture is still considered by some as first-line therapy for cartilage repair, is easily available, and is widely used clinically, thus reflecting a pragmatic "real-world" experience.

At baseline arthroscopic surgery (performed <8 weeks from screening) to assess the cartilage lesion and surrounding cartilage, a cartilage biopsy specimen (~200 mg) was harvested from a minor or nonweightbearing healthy area of the femoral condyle from all patients. After biopsies, patients were intraoperatively randomized, using an interactive voice response system and computer-generated 1:1 randomization scheme, to MACI or arthroscopic MFX.

For patients randomized to the MACI procedure, the biopsy specimens were sent to Genzyme Biosurgery (Cambridge, Massachusetts, USA), where autologous chondrocytes were isolated, cultured, and seeded onto a purified, resorbable, porcine-derived collagen type I/III membrane (ACI-Maix, Matricel GmbH). The final MACI product was a 20-cm^2 (5 $\times$ 4 cm) membrane seeded with 500,000 to 1 million cells/cm^2.

The MACI implantation procedure was performed via mini-arthrotomy 4 to 8 weeks after baseline arthroscopic surgery. Briefly, the lesions were debrided to a vertical rim of stable healthy cartilage without breaching the subchondral bone. The shape and size of the lesion(s) were assessed, and a template for each lesion was created. The MACI implant was trimmed to the correct size and shape of the defect and placed down into the debrided base of the defect with the cells facing the subchondral bone. The implant was secured in place using a thin layer of fibrin sealant on the base and edges of the defect, and stability of the implant was checked while fully extending and flexing the knee several times.

Microfracture was performed at the time of arthroscopic surgery strictly according to the technique described by Steadman et al.[34] Briefly, after debridement (as above), multiple holes (centers 3-4 mm apart and 4 mm deep) were made in the subchondral bone with a sharp surgical awl. The cartilage specimens obtained during biopsy were cryopreserved in the laboratory in the event that any patient required later MACI treatment. The patients' first follow-up visit was 6 weeks after MFX or MACI implantation (second stage).

Second-look arthroscopic surgery was used to assess the knee joint according to the International Cartilage Repair Society (ICRS) macroscopic evaluation criteria and obtain a biopsy specimen of repair tissue at year 2.

Rehabilitation

The 4-phase standardized rehabilitation program was based on a report by Steadman et al[33] and was the same for both treatments but individualized for each patient. On the basis of physical therapists' assessments, patients progressed through the program at different rates dependent on lesion size, lesion location, preoperative duration of symptoms, physical condition, patient motivation, and the expected course of healing for the procedure employed. Only when certain goals were reached at the end of each rehabilitation stage were the patients allowed to progress to the next stage. Rehabilitation phases are described in the Appendix (available in the online version of this article at http://ajsm.sagepub.com/supplemental).

Study Endpoints

The primary efficacy analysis was based on the co–primary endpoint of change from baseline to year 2 for the patient's KOOS pain and function (sports and recreational activities) subscores. One of the secondary endpoints was the patient's response rate to treatment based on the KOOS pain and function subscores at year 2. A responder was defined as having at least a 10-point improvement in both the KOOS pain and function subscales, whereas anyone not meeting both criteria was regarded as a nonresponder. Other endpoints are listed in Table 1.

Other predefined endpoints included the histological evaluation of structural repair biopsy specimens, as measured by the microscopic ICRS II overall assessment; magnetic resonance imaging (MRI) assessment of the degree of defect fill, as measured by the scale of the Whole Organ MRI Score (WORMS: 0%-25%, 26%-50%, 51%-75%, 76%-100%)[28] (the Magnetic Resonance Observation of Cartilage Repair Tissue [MOCART] scoring system[19] was not available at the time of study design); and treatment failure rate. Histology and MRI measures were evaluated in a blinded fashion by independent experts in pathology and radiology, respectively. Patients were defined as having a treatment failure if, at any time after week 24, they had a patient and physician global assessment result that was the same or worse than at baseline, a <10% improvement in the KOOS pain subscale, physician-diagnosed failure ruling out all other potential causes,

TABLE 1
SUMMIT Trial Endpoints[a]

Endpoint	Description
Co-primary (month 24)	Change from baseline in KOOS pain and function (sports and recreational activities) subscores
Secondary (month 24)	Histology (ICRS II)[17]
	Assessment of defect fill by magnetic resonance imaging
	Responder rate based on KOOS pain and function (≥10-point improvement) subscales
	Treatment failure rate
	Other KOOS subscales (activities of daily living, knee-related quality of life, and other symptoms)
Tertiary	At weeks 24, 36, 52, and 78:
	Change in all KOOS subscales
	Response rate
	Treatment failure
	Other clinical assessments:
	Modified Cincinnati Knee Rating System[26]
	International Knee Documentation (IKDC)[14]
	Quality of life assessments (months 24 and 48):
	12-Item Short Form Health Survey (SF-12)[37]
	European Quality of Life (EuroQol)–5 dimensions questionnaire (EQ-5D)
	Macroscopic ICRS "Cartilage Repair Assessment" (month 48)
Safety	Treatment-emergent adverse events
	Serious adverse events
	Subsequent surgical procedures

[a]ICRS, International Cartilage Repair Society; KOOS, Knee Injury and Osteoarthritis Outcome Score; SUMMIT, Demonstrate the Superiority of MACI implant to Microfracture Treatment.

and the physician deciding that surgical retreatment was needed. Physician-identified treatment failure cases were further evaluated by an independent treatment failure evaluation committee that reassessed whether each case met the treatment failure criteria.

Patients were evaluated for adverse events at each study visit. An adverse event was defined as any undesirable physical, psychological, or behavioral effect experienced by a patient, independent of treatment relatedness. Adverse events were categorized using the Medical Dictionary for Regulatory Activities, recorded by severity, duration, and treatment relationship. Subsequent surgical procedures were those performed on the target knee during the study; subsequent surgical procedures were not necessarily considered treatment failure but were classified as a serious adverse event. Planned second-look arthroscopic surgeries performed at the 2-year follow-up were not identified as subsequent surgical procedures.

Statistical Analysis

To power the study at 85% to detect a difference between groups, a total sample size of 144 patients (72 patients per arm) was estimated based on the change from baseline to year 2 in the co–primary efficacy endpoint of the KOOS pain and function subscales with an α of .05 (and accounting for patient discontinuation), assuming a difference of 12 points each for the KOOS pain and function subscores with standard deviations of 20 and 30, respectively, and a correlation coefficient of 0.56 between the co–primary variables.

All randomized and treated patients were analyzed. The co–primary endpoint of change in the KOOS pain and function subscales from baseline to year 2 was analyzed with SAS (SAS Institute, Cary, North Carolina, USA) using a multivariate analysis of variance (MANOVA) model and last observation carried forward (LOCF) for missing data imputation. The final MANOVA model included treatment, study site, and baseline KOOS values. The Wilks λ test statistic and associated single P value from the MANOVA model were used to test the statistical significance of the difference in the co–primary endpoint between MACI and MFX. All other changes in the KOOS subscales at all other time points were analyzed and compared between MACI and MFX using analysis of variance (ANOVA) and LOCF. Individual P values for the change from baseline to 2 years for pain and function were also reported; however, that analysis was not part of the a priori statistical analysis plan. Differences between groups were tested by MANOVA and the Cochran-Mantel-Haenszel χ^2 test for histology and by the Cochran-Mantel-Haenszel χ^2 test for responders and defect fill. The Cochran-Mantel-Haenszel χ^2 test was also used to analyze differences in response rates between groups by lesion size, lesion location, and OCD origin.

Predictor variables were also tested post hoc on the co–primary endpoint changes from baseline using multivariate analysis of covariance (MANCOVA), with treatment and center as fixed effects and baseline KOOS pain and function subscores, age, total defect size, occurrence of previous surgery, duration of symptoms, and index lesion location as covariates. Only significant covariates at a .05 level were included in the final model. The Wilks λ test statistic and associated P value were used to test the statistical significance for the co–primary endpoint between MACI and MFX.

TABLE 2
Patient and Lesion Characteristics[a]

	MACI (n = 72)	Microfracture (n = 72)
Patients		
Age, mean ± SD, y	34.8 ± 9.2	32.9 ± 8.8
Male sex, %	62.5	66.7
Body mass index, mean ± SD, kg/m^2	26.2 ± 4.3	26.4 ± 4.0
Duration of symptoms, mean (range), y	5.8 (0.05-28.0)	3.7 (0.1-15.4)
Baseline KOOS pain, mean ± SD	37.0 ± 13.5	35.5 ± 12.1
Baseline KOOS function, mean ± SD	14.9 ± 14.7	12.6 ± 16.7
Lesions		
Index lesion size, mean ± SD, cm^2	4.9 ± 2.8	4.7 ± 1.8
Total defect surface area, mean ± SD, cm^2	5.8 ± 5.1	5.3 ± 2.5
Location, n (%)		
MFC	54 (75.0)	53 (73.6)
LFC	13 (18.1)	15 (20.8)
Trochlea	5 (6.9)	4 (5.6)
Origin, n (%)		
Acute trauma	33 (45.8)	45 (62.5)
Chronic degeneration	18 (25.0)	9 (12.5)
Osteochondritis dissecans	8 (11.1)	12 (16.7)
Unknown	9 (12.5)	6 (8.3)
Other	4 (5.6)	0
Outerbridge grade, n (%)		
III	21 (29.2)	15 (20.8)
IV	51 (70.8)	57 (79.2)
Lesion containment, n (%)		
Completely contained	50 (69.4)	46 (63.9)
Partially contained	22 (30.6)	26 (36.1)

[a]KOOS, Knee Injury and Osteoarthritis Outcome Score; LFC, lateral femoral condyle; MACI, matrix-applied characterized autologous cultured chondrocytes; MFC, medial femoral condyle.

RESULTS

Patient and Lesion Characteristics

A total of 144 patients were enrolled and treated with MACI (n = 72) or MFX (n = 72) (Figure 1). Most of the patients (95%; 137/144) completed a full 2 years of the study. No patients treated with MACI discontinued because of a lack of efficacy compared with 3 patients treated with MFX (Figure 1). Patients had a mean age of 33.8 years and a mean body mass index of 26 kg/m^2, and 65% were male (Table 2). The mean baseline values for the KOOS pain and function subscales were 37.0 and 14.9 in the MACI arm and 35.5 and 12.6 in the MFX arm, respectively.

Lesions had a mean size of 4.8 cm^2 (range, 3-20 cm^2), and most were located on the MFC or LFC and were completely contained (Table 2). Acute trauma was the most common underlying cause of the lesions (54.2%), followed by chronic degeneration (18.8%) and OCD (13.9%).

The most common prior procedures were diagnostic arthroscopic surgery (50.3%), marrow stimulation techniques (34.6%), debridement of the lesion (26.3%), and loose body removal (23.2%) (see Appendix Table A1, available online). The most common concomitant procedures during the index biopsy or implantation were loose body removal, partial medial meniscectomy, and synovectomy/synovial plica excision (see Appendix Table A1).

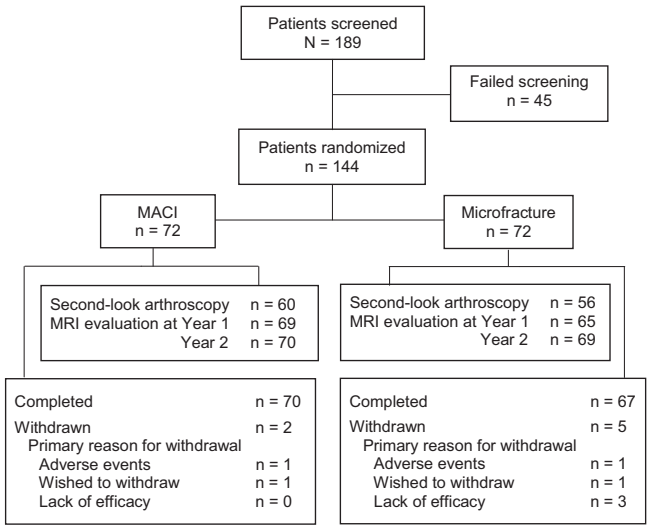

Figure 1. Patient characterisitics.

KOOS Pain and Function

Two years after treatment, the improvement seen in MACI over MFX with regard to the co–primary endpoint was clinically and statistically significant (P = .001), with the

TABLE 3
Scores for Patient-Reported Outcomes With MACI and Microfracture at Baseline and Year 2[a]

	MACI				Microfracture					
	n	Baseline	n	Year 2	n	Baseline	n	Year 2	Estimated Mean Difference	P^b
KOOS subscales										
Pain	72	37.0 ± 13.5	72	82.5 ± 16.2	71	35.5 ± 12.1	70	70.9 ± 24.2	11.76	.001[c]
Function	72	14.9 ± 14.7	72	60.9 ± 27.8	71	12.6 ± 16.7	70	48.7 ± 30.3	11.41	
Activities of daily living	72	43.5 ± 18.2	72	87.2 ± 16.5	72	42.6 ± 19.6	71	75.8 ± 24.2	12.01	<.001
Knee-related quality of life	72	18.8 ± 14.7	72	56.2 ± 23.9	72	17.2 ± 14.1	71	47.3 ± 27.0	8.98	.029
Other symptoms	72	48.3 ± 16.9	72	83.7 ± 14.0	72	44.4 ± 18.6	71	72.2 ± 19.5	11.61	<.001
Modified Cincinnati Knee Rating System	72	3.0 ± 1.2	72	6.4 ± 2.1	72	3.0 ± 1.2	71	5.4 ± 2.2	1.05	.002
IKDC subjective knee evaluation	71	32.9 ± 13.3	72	65.7 ± 18.5	72	29.3 ± 13.4	71	58.8 ± 22.3	5.94	.069
SF-12 physical component score	72	–1.77 ± 0.86	72	–0.32 ± 0.89	69	–1.93 ± 0.82	71	–0.82 ± 1.12	0.51	.001
SF-12 mental component score	72	0.04 ± 1.2	72	0.45 ± 0.9	69	–0.17 ± 1.3	71	0.49 ± 1.0	–0.09	.523
EQ-5D visual analog scale	72	60.8 ± 20.9	72	77.5 ± 15.3	72	56.2 ± 22.1	70	73.4 ± 18.4	3.75	.148

[a]Values are expressed as mean ± standard deviation unless otherwise specified. EQ-5D, European Quality of Life (EuroQol)–5 dimensions questionnaire; IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; MACI, matrix-applied characterized autologous cultured chondrocytes; SF-12, 12-Item Short Form Health Survey.

[b]*P* value for difference between treatments in estimated means for change from baseline to year 2.

[c]Wilk λ *P* value for co–primary endpoint (KOOS pain and KOOS function) for difference between treatments in estimated means for change from baseline to year 2.

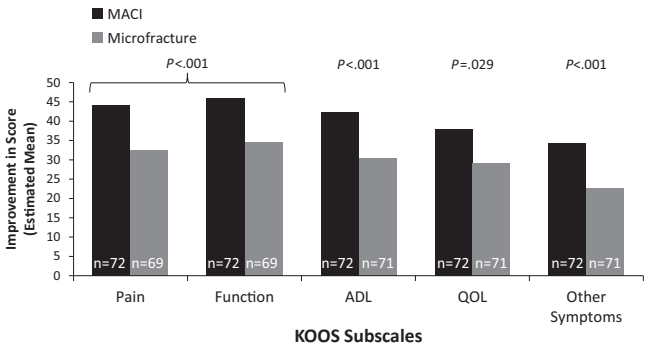

Figure 2. Changes from baseline to year 2 in all Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales for patients treated with the matrix-applied characterized autologous cultured chondrocytes (MACI) implant or microfracture.

estimated mean difference in the KOOS pain subscore being 11.76 ($P < .001$) and function subscore being 11.41 ($P = .016$) (Table 3). Changes in the KOOS pain and function subscales at year 2 are shown in Figure 2. The significant improvement for MACI over MFX was observed for the KOOS pain and function subscales as early as 36 weeks ($P < .03$) and was maintained at 52 weeks ($P < .025$) (Figure 3) and out to 104 weeks.

The percentage of patients who responded to treatment at year 2 (Figure 4) was significantly greater ($P = .016$) with MACI (87.5%) than with MFX (68.1%). Also, MACI and MFX nonresponders comprised 12.5% and 31.9%, respectively.

The predictors' subanalysis of the response rates by patient characteristics showed that significantly more patients responded with MACI than with MFX when patients were male, had a median age <34.5 years, only had 1 lesion, had lesions resulting from acute trauma, underwent 1 prior surgery, or had a duration of symptoms lasting >3 years (see Appendix Table A2). Response rates between patients with or without prior cartilage surgeries were similar. When analyzed by lesion characteristics, significantly more patients responded with MACI compared with MFX when their lesions were >4 cm^2 in size and located on the MFC.

Other Clinical Outcomes

In year 2, the mean improvements from baseline in the other KOOS subscales (activities of daily living, knee-related quality of life, and other symptoms) were significantly better for patients treated with MACI versus MFX ($P < .001$, $P = .029$, and $P < .001$, respectively) (Figure 2). At 52 and 78 weeks, mean improvements were significantly better for all KOOS subscales for MACI versus MFX. Improvements from baseline were significantly better for the modified Cincinnati Knee Rating System scores at years 1 and 2 ($P = .018$ and $P = .002$, respectively) and for the IKDC score at year 1 ($P = .009$), favoring MACI over MFX (Table 3).

Significantly better improvements from baseline to year 1 and 2 ($P = .029$ and $P = .001$, respectively) were observed for the 12-Item Short Form Health Survey (SF-12) physical component score but not the mental component score (Table 3). Increases in the European Quality of Life (EuroQol)–5 dimensions questionnaire (EQ-5D) visual analog scale scores from baseline to year 2 were similar for both groups. No significant difference in the mean improvement of the overall health status was seen at year 1 or at year 2 from baseline.

No analyses were conducted for treatment failure rates between treatment groups because of the small number of treatment failures. Only 2 patients in the MFX group were

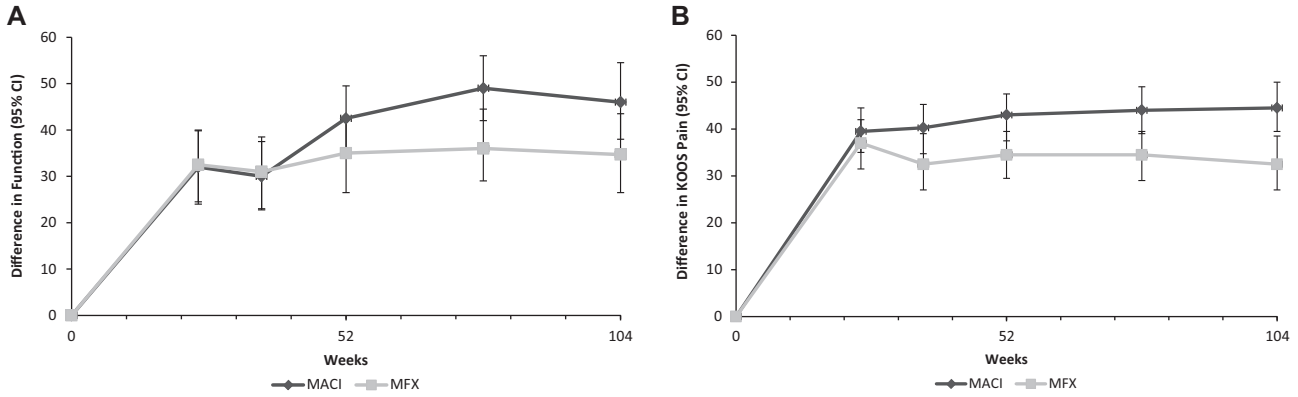

Figure 3. Mean (95% CI) improvement in the Knee Injury and Osteoarthritis Outcome Score (KOOS) function (A) and pain (B) subscales over time for patients treated with the matrix-applied characterized autologous cultured chondrocytes (MACI) implant or microfracture. A significant improvement ($P < .030$) was observed with MACI compared with microfracture for the KOOS function and pain subscales at year 1, which was maintained to year 2 ($P < .025$).

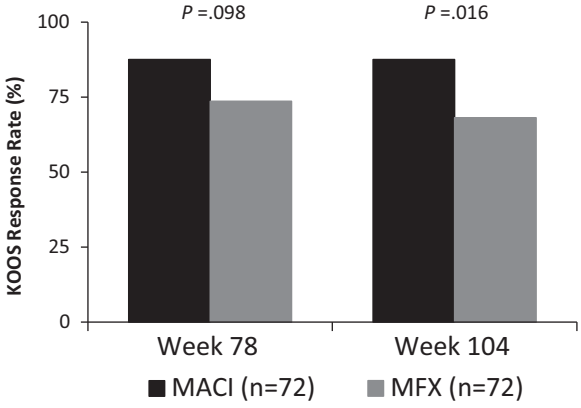

Figure 4. Percentage of patients who responded (≥10-point improvement in the Knee Injury and Osteoarthritis Outcome Score [KOOS] pain and function subscales at year 2).

deemed treatment failures, and no patients in the MACI group were considered treatment failures.

Repair Tissue Assessment

One hundred sixteen patients (MACI, n = 60; MFX, n = 56) underwent second-look arthroscopic surgery and biopsy (Figure 1). Overall, structural repair tissue was very good for both treatments. The mean microscopic ICRS II overall assessment score between groups (63.8 vs 62.3, respectively; estimated mean difference, 1.52) was not significantly different ($P = .717$).

Repair tissue assessment at year 2 with the macroscopic ICRS II cartilage repair scores showed similar results between groups, with no significant difference in the overall repair assessment, degree of defect repair, graft integration to border zones, and macroscopic appearance (Table 4). Approximately 76% of patients in the MACI group had normal or nearly normal (grade I/II) results for the overall repair assessment versus 60% of patients in the MFX group. The majority of patients had a degree of defect repair that was in line with the surrounding cartilage, showed graft integration to border zones that was either complete or with a <1-mm demarcating border, and had repair tissue with an intact smooth or fibrillated surface.

The MRI evaluation of structural repair was performed in 134 patients at year 1 and in 139 patients at year 2 (Figure 1). The MRI evaluation of structural repair at year 1 and 2 showed improvement in defect filling for both treatments but with no statistically significant differences. At year 2, 83% of patients who had MACI and 77% of patients who had MFX showed a degree of defect fill that was >50% of the defect depth.

Safety

No unexpected safety events were reported. Treatment-emergent adverse events (TEAEs) were observed in 55 patients (76.4%) in the MACI group and 60 patients (83.3%) in the MFX group. Most TEAEs were of moderate or mild intensity. The most common TEAEs (Table 5) were arthralgia (57.6%), headache (23.6%), and nasopharyngitis (11.8%). The incidence of TEAEs considered to be related to the study treatment was comparable between treatments (MACI: 34.7% and MFX: 38.9%). The most common related TEAEs were treatment failure, arthralgia, and joint swelling. In each group, 1 patient (1.4%) discontinued because of TEAEs.

Serious TEAEs were reported more frequently in the MFX group (26.4%) than in the MACI group (15.3%), which were attributed to treatment failure, cartilage injury, and arthralgia in the MFX group. No deaths occurred in this study.

The number of patients with at least 1 subsequent surgical procedure was not significantly different ($P = .427$) between the MACI group (8.3%) and the MFX group (9.7%). Two subsequent surgical procedures were experienced by 2 patients in the MFX group but by no patient in the MACI group. Increasing age significantly decreased

TABLE 4
Macroscopic ICRS Cartilage Repair Assessment Scores[a]

	MACI (n = 72)	Microfracture (n = 72)	*P*
Overall repair assessment			.145
Grade I (normal)	14 (19.4)	8 (11.1)	
Grade II (nearly normal)	41 (56.9)	35 (48.6)	
Grade III (abnormal)	4 (5.6)	12 (16.7)	
Grade IV (severely abnormal)	5 (6.9)	4 (5.6)	
Missing	8 (11.1)	13 (18.1)	
Degree of defect repair			.430
In line with surrounding cartilage	45 (62.5)	38 (52.8)	
75% repair of defect depth	10 (13.9)	9 (12.5)	
50% repair of defect depth	4 (5.6)	7 (9.7)	
25% repair of defect depth	4 (5.6)	3 (4.2)	
0% repair of defect depth	1 (1.4)	2 (2.8)	
Missing	8 (11.1)	13 (18.1)	
Graft integration to border zones			.519
Complete integration	21 (29.2)	15 (20.8)	
Demarcating border <1 mm	20 (27.8)	20 (27.8)	
3/4 integrated, 1/4 with border >1 mm	14 (19.4)	13 (18.1)	
1/2 integrated, 1/2 with border >1 mm	3 (4.2)	7 (9.7)	
No contact to 1/4 integrated	6 (8.3)	4 (5.6)	
Missing	8 (11.1)	13 (18.1)	
Macroscopic appearance			.164
Intact smooth surface	25 (34.7)	16 (22.2)	
Fibrillated surface	21 (29.2)	22 (30.6)	
Small, scattered fissures	13 (18.1)	13 (18.1)	
Several small or few but large fissures	3 (4.2)	5 (6.9)	
Total degeneration of grafted areas	2 (2.8)	3 (4.2)	
Missing	8 (11.1)	13 (18.1)	

[a]Values are expressed as n (%). ICRS, International Cartilage Repair Society; MACI, matrix-applied characterized autologous cultured chondrocytes.

the likelihood of at least 1 subsequent surgical procedure occurring ($P = .038$).

DISCUSSION

Our study demonstrates that MACI is clinically and statistically significantly better than MFX for treating symptomatic cartilage defects of the knee, meeting our study's predefined co–primary endpoint. Overall, patients treated with MACI had superior KOOS subscores for all 5 subscales than patients treated with MFX after 2 years. Additionally, significantly more patients in the MACI group had ≥10-point improvement in their KOOS pain and function subscores versus those in the MFX group. Scores for the modified Cincinnati Knee Rating System and SF-12 physical component scores also improved significantly more with MACI than with MFX. In addition, no treatment failures were reported for the MACI group compared with 2 in the MFX group. Further, repair tissue with MACI also showed good structural outcomes, although not statistically different than with MFX. Finally, the safety profile was similar between the groups, and no unexpected safety issues were encountered.

Our better clinical outcomes with MACI versus MFX are consistent with the results from a recent smaller randomized trial in which treated symptomatic chondral defects of the femoral condyle or patella (N = 60) showed that the Lysholm, Tegner, and patient and surgeon ICRS scores improved significantly more with MACI than with MFX after 2 years.[2] In a case series (N = 34), the

TABLE 5
Most Frequently Reported (>5%) TEAEs[a]

	MACI (n = 72)	Microfracture (n = 72)
Any TEAE	55 (76.4)	60 (83.3)
Arthralgia	37 (51.4)	46 (63.9)
Headache	13 (18.1)	21 (29.2)
Nasopharyngitis	10 (13.9)	7 (9.7)
Back pain	8 (11.1)	7 (9.7)
Joint swelling	7 (9.7)	4 (5.6)
Joint effusion	5 (6.9)	4 (5.6)
Influenza	4 (5.6)	5 (6.9)
Pyrexia	4 (5.6)	2 (2.8)
Cartilage injury	3 (4.2)	9 (12.5)
Procedural pain	3 (4.2)	4 (5.6)
Ligament sprain	2 (2.8)	4 (5.6)
Abdominal pain	0 (0.0)	5 (6.9)

[a]Values are expressed as n (%). MACI, matrix-applied characterized autologous cultured chondrocytes; TEAE, treatment-emergent adverse event.

Lysholm-Gillquist score also improved by more points with MACI than with MFX (48 vs 29, respectively).[1]

Good clinical outcomes reported with MACI in our study are also similar to those reported in previous MACI implant case series.[6-8,18] Marlovits and colleagues[18] reported good clinical outcomes with few complications and a low rate of treatment failure in a 5-year follow-up study of patients treated with MACI. Consistent with our study, the patients had significant improvements from baseline on all KOOS subscales, modified Cincinnati Knee Rating System, and IKDC as well as significant improvements in the Tegner-Lysholm scores as early as 1 year after treatment.[18]

In the previous studies described above that reported safety, MACI provided a good safety profile, similar to our study.[2,7,18] In one study, typical postoperative swelling and effusion were observed in patients but resolved within 4 weeks of the MACI procedure.[18] In another study, 2 patients developed deep vein thrombosis early after treatment, while 1 patient developed a postoperative hematoma; all patients recovered without sequelae.[7] In all of the studies, no deaths occurred.[2,7,18]

Beneficial results with MFX here are also consistent with those of previous MFX studies showing good clinical outcomes[12,32]; however, some reports showed that such improvements with MFX are not always sustained past 18 to 24 months.[15,16,23,25]

Our analysis of predictors by the response rate showed that more patients with a longer duration of symptoms (>3 years) or younger age (median, <34.5 years) improved with MACI when compared with MFX. However, Vanlauwe and colleagues[36] found that patients with less time since symptom onset (<3 years vs ≥3 years) did better with characterized chondrocyte implantation (CCI) than with MFX, while cell therapy in older defects did not seem to have an added benefit. Furthermore, no discernible difference was observed between younger (<35 years) and older (≥35 years) patients.[36] In another study, younger patients (<30 years) had better clinical outcomes than older patients, regardless of treatment with MACI or MFX.[15] The reasons for the inconsistencies in our results compared with findings in these previous studies are unknown but may pertain to patient population, lack of statistical power among the subgroups, or technique differences.

Structural endpoints assessed by MRI and repair tissue histology assessed by the ICRS II score demonstrated good quality repair tissue with MACI. However, good quality repair tissue with MACI was not different than that found with MFX, even given the clinical results favoring MACI. These findings were unexpected in that MFX structural scores were better than anticipated, as previous studies showed better repair tissue with autologous cell therapies than with MFX. However, it should be noted that the study's power was based on the primary clinical endpoint, and the study was not powered to show a statistical difference on secondary structural endpoints. In a study by Bachmann and colleagues,[1] the MRI-evaluated repair tissue was of better quality, with the defect fill being more consistent, and better integrated with the adjacent cartilage with MACI (n = 27) than with MFX (n = 7). These authors also found that the MRI signal intensity of the repair tissue with MACI was close to that of the surrounding native cartilage, whereas the signal intensity was different than that of adjacent normal cartilage with MFX.

Other studies showed better repair tissue with other cell therapy technologies than with MFX. One year after CCI, structural repair tissue was better than with MFX,[30] as shown by better mean histology assessment (blinded) scores (P = .012) and more intense safranin O and collagen II stainings (P = .03).[30] However, MRI assessment showed similar repair tissue after 3 years,[29] with no report on repair tissue at year 5.[36]

The reasons for our unanticipated similar results in structural repair tissue between MACI and MFX are currently unknown. The clinical relevance, reproducibility, and applicability to long-term clinical outcomes of the ICRS II, a recently developed histology grading system for cartilage repair, still need to be established.[17] Further, one cannot ensure that biopsy specimens taken were the best representative sample of the total repair tissue especially because the samples were taken by individual surgeons and not by 1 dedicated sampling person, although this would apply equally to both groups.[24] Evidence for the "overperformance" of MFX in the present study can be found in a study comparing MFX with CCI, as our overall ICRS II score with MFX (62.3) was numerically higher than that in the MFX-CCI comparison (~44).[30] Finally, the study protocol was designed so that all MRI readings, including preoperative reads, were blinded from a treatment and temporal perspective to minimize reader bias.

Additional longer term comparative studies are needed to further understand the relationship between clinical outcomes and integrity of the structural cartilage tissue. A systematic review and meta-analysis reported by de Windt et al[5] found that the majority of articular cartilage repairs in knee studies showed limited or no correlation between clinical outcomes and MRI parameters; only 28% of studies (9/32) showed a correlation between clinical outcomes and MOCART or Henderson scores. This is in line with guidance from regulatory agencies (EMA and FDA) that suggests that MRI data, as well as histology data, are not predictive of outcomes and that clinical outcomes assessing pain and function are the most important parameters in determining the efficacy of cell-based therapies.[9,35] Nevertheless, an extension of our study is currently underway in which 3- and 5-year outcomes will be assessed.

Some of the limitations of this study include the fact that the procedures were performed by many surgeons and that it was not a blinded study. However, all surgeons were trained on standardized surgical procedures, and their training was audited by the sponsor. In addition, given that the surgical techniques for MACI (2 surgeries) and MFX (1 surgery) are different, the study could not be blinded; however, histological and MRI evaluations were assessor blinded. Because of the inherent heterogeneity of cartilage repair tissue, one limitation of the histological evaluation is the inability to ensure that the biopsy specimen acquired was representative of the total cartilage repair tissue.[24] Also, it is possible that the favorable results

observed for patients in both treatment groups could have been positively influenced by the rigorous patient education and follow-up inherent in the study protocol.

Our SUMMIT clinical trial is one of the very few GCP-conducted, prospective, multicenter, randomized controlled studies of cell-based cartilage repair to date. The study included stringent inclusion and exclusion criteria, standardized surgical and rehabilitation procedures, and validated clinical outcome instruments and ensured a comprehensive patient follow-up. Other strengths of the study included the use of histology and MRI assessments.

Overall, improvements in clinically relevant endpoints such as pain and function, as opposed to those of structural repair, remain the more important endpoints for the study of cartilage defects with regard to patient care.[24] This trial demonstrated that at 2-year follow-up, MACI provides significantly better pain relief and functional improvement when compared with MFX in this heterogeneous population, with similarities in repair and safety profiles, when treating symptomatic articular cartilage defects ≥ 3 cm^2 of the knee.

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