

Clinical Outcomes of Characterized Chondrocyte Implantation

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Abstract

Objective: To assess the clinical outcome of patients treated with autologous chondrocyte implantation using ChondroCelect in daily practice. **Methods:** The study is a cross-sectional analysis of an open-label, noninterventional cohort. The setting was a compassionate use program, involving 43 orthopaedic centers in 7 European countries. The participants were patients treated with ChondroCelect between October 13, 2004 and July 2, 2008. The measurements used were Clinical Global Impression–Improvement and –Efficacy and solicited adverse event reports. **Results:** Safety data were collected from 334 patients (90.3%), and effectiveness data were from 282 (76.2%) of the 370 patients treated. Mean age at baseline was 33.6 years (range, 12–57 years), 57% were male, and mean body mass index was 25 kg/m². Mean follow-up was 2.2 years (range, 0.4–4.1 years). A femoral condyle lesion was reported in 66% (288/379) and a patellar lesion in 19% (84/379). Mean lesion size was 3.5 cm²; a collagen membrane was used in 92.4% (328/355). A therapeutic effect was reported in 89% (234/264) of patients overall and in 87% (40/46) of patellar lesion patients. Rates of much or very much improved patients were similar in patients with short- (<18 months: 71% [115/163]) and long-term follow-up (>18 months: 68% [70/103]) ($P = 0.68$) and were independent of lesion size (>4 cm²: 75.5% [37/49]; ≤4 cm²: 67.7% [111/164]) ($P = 0.38$). Adverse events were similar to those reported in the randomized trial with the same product, with more arthrofibrosis, more reduced joint mobility, and more crepitations reported in patellar lesions. Overall, less cartilage hypertrophy was noted, probably due to the use of a biological membrane cover. **Conclusions:** Implantation of ChondroCelect appeared to result in a positive benefit/risk ratio when used in an unselected heterogeneous population, irrespective of the follow-up period, lesion size, and type of lesion treated.

Keywords

chondrocyte implantation, autologous, ACI, ChondroCelect, patella, clinical

Introduction

Autologous chondrocyte implantation (ACI) is a well-established option in the treatment of symptomatic grade III or IV cartilage lesions of the knee.^{1,2} As cartilage lesions tend not to heal spontaneously, ACI aims to regenerate healthy cartilage tissue by surgically implanting *ex vivo*-cultured autologous chondrocytes in the defect site.³ ChondroCelect (TiGenix, Leuven, Belgium) is the first and only advanced therapy medicinal product (ATMP) consisting of characterized chondrocytes to obtain a European Union marketing authorization from the European Medicine Agency (EMA). This approval was based on randomized study data in selected patients with single symptomatic cartilage lesions of the femoral condyle, demonstrating better structural repair at 12 months in comparison to microfracture⁴ and a favorable benefit/risk ratio of ChondroCelect implantation.⁵ However, results of randomized controlled

trials (RCTs) may not necessarily be applicable to the general population.^{3,4,6–8} The objective of this study was to assess whether this favorable benefit/risk ratio could be

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extrapolated to a broader population reflecting daily clinical practice, based on data from a compassionate use program (CUP) conducted prior to marketing authorization.

As lesions larger than 5cm² and multiple, salvage and patellar lesions were excluded from the randomized study with ChondroCelect, we were particularly interested to assess the safety and the benefit/risk balance in this non-randomized CUP population.

Methods

This was an open-label, noninterventional CUP, based on written patient-named prescriptions by an orthopedic surgeon, provided that written informed consent was given by the patient. The program was conducted in accordance with the Declaration of Helsinki. Ethics committees were notified, and competent authorities were involved according to national guidance and legislation.

Patients with symptomatic articular cartilage defect(s) of the knee could be included in the ChondroCelect CUP. There were no predefined eligibility criteria for entry into the study, and no prospectively defined outcome measures were assessed. A defect size report was required for each individual patient in order to calculate the dose of ChondroCelect to be provided for implantation, and surgeons were trained in the use of ChondroCelect as part of the routine educational program, which was implemented for the product. The Summary of Product Characteristics (SPC #203) indicated a preliminary therapeutic indication and mentioned that implantation of the cells should be followed by an appropriate rehabilitation schedule, protecting the graft from early damage.

Patients in whom an active infection was identified at the time of biopsy could not have their chondrocytes expanded and were therefore excluded from treatment with ChondroCelect. Furthermore, ChondroCelect was not for use in the treatment of cartilage damage associated with significant osteoarthritic lesions. ChondroCelect was not to be used in patients with a known history of hypersensitivity to penicillin G, streptomycin sulfate, and amphotericin B as well as having hypersensitivity to products of bovine origin.

During the ACI procedure, according to Brittberg *et al.*,³ approximately 4 weeks after arthroscopy, the cartilage defect was debrided back to stable borders to obtain a contained lesion wherever possible, and ChondroCelect was implanted beneath a biological membrane (either autologous periosteum or Chondro-Gide [Geistlich, Wolhusen, Switzerland]) and sutured over the defect, assuring a watertight seal.⁹ ChondroCelect was administered at an intended dose of 0.8 to 1.0 million cells/cm². The amount of ChondroCelect delivered into the cartilage defect during ACI depended on the size of the defect.

ChondroCelect is a suspension of characterized viable autologous cartilage cells obtained from the *in vitro* expansion of autologous human chondrocytes. The source chondrocytes are isolated from a small biopsy of articular cartilage and harvested from a lesser weightbearing zone in the patients' afflicted knee during arthroscopy. The cell product has been extensively characterized for *in vivo* tissue formation, production of important cartilage matrix proteins and proteoglycans, and cellular expression patterns of genes relevant for cartilage and chondrocyte biology. Based on this comprehensive characterization, the manufacturing process has been specifically designed to produce phenotypically stable expanded chondrocytes with the best potential to regenerate stable repair cartilage *in vivo*. Each single-use container of autologous cultured chondrocytes contains 4 million cells. To manufacture ChondroCelect, knowledge of the size of the lesion was required as well as evidence of negative serology test results for HIV, hepatitis B and C, and syphilis.

All patients who were eventually treated with ChondroCelect in the CUP between October 13, 2004 and July 2, 2008 were identified and listed per surgeon. Detailed demographic and medical data were not collected systematically in all CUP patients. Between November 2008 and January 2009, each surgeon was requested to provide a duly completed adverse event (AE) collection sheet per patient with all clinically relevant, knee-related AEs, as well as a Clinical Global Impression scale of improvement (CGI-I) and efficacy (CGI-E) for each patient, retrospectively derived from previous follow-ups. For each AE, the start and stop dates, the outcome, severity, and relationship to ChondroCelect and to the study procedure were requested as well as the seriousness and the action taken. All reported serious adverse events (SAEs), both knee related and not knee related, were also collected.

The CGI-I is a 7-point categorical scale with 3 categories of improvement and 3 categories of worsening (minimally, much, and very much), centered around a category of "no change".¹⁰ The CGI-E is a 4-point scale with the categories "very good", "moderate", "slight", and "unchanged or worse".¹⁰ Both CGI-I and CGI-E are surgeon-rated scales. Whereas the CGI-I intends to measure the clinical global impression of the clinician with respect to the improvement (or worsening) of the patient since baseline or presurgery, the CGI-E rates the clinician's global impression of the patient's degree of improvement that is considered to be related to the intervention only. The results were assessed also in patients with short-term (0 ≤ 18 months; mean = 9 months; standard deviation [SD] = 4.58 months) and midterm follow-ups (>18 months; mean = 27 months; SD = 6 months).

Safety data and surgeon-assessed CGI scores were collected between December 15, 2008 and January 7, 2009.

Table 1. Patient Flow Chart

No. of patients biopsied	N = 399	
Full Analysis Set (FAS): no. of patients implanted	n = 370	Implantation was not performed in 29 patients: no or insufficient cells isolated from biopsy (n = 12), the cells stopped growing (n = 11), patients eventually refused implantation or did not show at surgery (n = 4), positive sterility test result (n = 1), and low CC (ChondroCelect) score (n = 1).
Safety Analysis Set (SAS): no. of patients implanted	n = 334	For 36 patients, no safety data could be received.
Efficacy Data Set (EDS): no. of patients implanted	n = 282	For 52 patients, no Clinical Global Impression (CGI) could be received.

The Full Analysis Set (FAS) included all patients treated, the Safety Analysis Set (SAS) included all patients for whom a safety assessment was received, and the Effectiveness Data Set (EDS) consisted of patients in whom effectiveness data were received. Continuous variables were summarized using descriptive statistics: number of observations, minima, maxima, means, medians, and SDs. Categorical variables were summarized using frequencies and percentages. Lesions were grouped according to their size in smaller (≤ 4 cm²) and larger (>4 cm²) lesions¹¹ and whether they were single or multiple. Comparisons of dichotomous outcomes between 2 groups were tested using the Fisher exact test (2 sided). A *P* value of >0.05 was considered not significant.

Results

There were 370 patients who had a ChondroCelect implantation (FAS) from a total of 399 patients in whom a biopsy was taken (**Table 1**). Safety data (SAS) were able to be collected from 334 patients (90.3%) and effectiveness data (EDS) from 282 patients (76.2%). The following number of patients participated per country: Belgium (*n* = 291), the Netherlands (*n* = 40), Germany (*n* = 16), Luxemburg (*n* = 2), United Kingdom (*n* = 17), Italy (*n* = 3), and Spain (*n* = 1). As 9 of the 370 patients were treated on 2 different lesions on 2 different occasions (2 separate lesions at different time points), a total of 379 treatments were administered. As not all reported parameters are available for all patients (e.g., age, gender), the denominator is variable. The SAS included only those patients for whom safety data were available at database lock (*n* = 334, fixed denominator). Gender was known in 184 patients: 93 male and 91 female patients (56.7% male). Mean age was 33.7 years (179/370 or 48.4% <40 years; range = 12-57 years), and the median body mass index (BMI) was 24.4 kg/m² (mean = 25.01 kg/m²) (**Table 2**). A condylar cartilage lesion (43.4% medial, 15.1% lateral, and 7.3% not specified) was reported in 288 (65.8%) of all reported lesions, a patellar lesion in 84 (19.2%), a trochlear lesion in 39 (8.9%), and a tibial lesion in 13 (3.0%); lesion

Table 2. Baseline Demographic and Medical Data

Demographic	
Age, mean (SD), y	33.7 (9.6)
Sex, % male	56.7
Weight, mean (SD), kg	77.1 (14.2)
Body mass index, mean (SD), kg/m ²	25.0 (3.4)
Cartilage lesion size, mean (range), cm ²	3.51 (0.25-20.0)
Cartilage lesion location, <i>n</i> (%)	
Medial femoral condyle	190 (43.3)
Patella	84 (19.2)
Lateral femoral condyle	66 (15.1)
Trochlea	39 (8.9)
Femoral condyle	32 (7.3)
Tibial plateau	13 (3.0)
Not specified	13 (3.0)
Single lesions	330 (87)
Multiple lesions	49 (13)

location was not disclosed in 11 patients (13 lesions: 3.5%). Lesion size was reported in 420 patients (95.9%) and ranged from 0.25 to 20.0 cm², with a median of 3.0 cm² (mean = 3.5 cm²); 164 of 213 lesions (77%) were 4 cm² or less, whereas 49 of 213 lesions of which CGI-E and -I were known were larger than 4 cm². In 316 of 370 or 85.4% of the patients, a single cartilage lesion was reported, 2 lesions in 42 of 370 or 11.4%, 3 lesions in 10 of 370 or 2.7%, and 2 patients (0.5%) had 4 lesions reported. A Chondro-Gide membrane was used in 328 of 355 or 92.4% of patients. Concomitant surgery included osteotomy in 18 of the 379 implantations (4.5%), anterior cruciate ligament (ACL) repair in 8 (2.1%), shaving and microfracture in 3 each (0.8%), and lateral release and meniscal repair in 2 each (0.5%). Three osteotomies were tibiofemoral, and 15 were patellofemoral Fulkerson type.¹² The average exposure, that is, the time between ChondroCelect implantation and database freeze was 811 days (range = 160-1512 days; SD = 330 days) for all treated lesions (*n* = 379).

Table 3. Clinical Global Impression–Improvement (CGI-I) and –Efficacy (CGI-E) According to Postoperative Period

CGI-I	EDS population				Total	CGI-I	Patella population		
	0-≤18 mo	>18 mo	Not known	Total			0-≤18 mo	>18 mo	Total
Very much improved	51 (31.3%)	28 (27.2%)	3 (%)	82 (29.8%)	Very much improved	10 (38.5%)	5 (25.0%)	15 (32.6%)	
Much improved	64 (39.3%)	42 (40.8%)	3 (%)	109 (39.6%)	Much improved	6 (23.1%)	7 (35.0%)	13 (28.3%)	
Minimally improved	29 (17.8%)	17 (16.5%)	1 (%)	47 (17.1%)	Minimally improved	6 (23.1%)	6 (30.0%)	12 (26.1%)	
No change	12 (7.4%)	6 (5.8%)	2 (%)	20 (7.3%)	No change	1 (3.8%)	0 (0.0%)	1 (2.2%)	
Minimally worse	5 (3.1%)	6 (5.8%)	0 (%)	11 (4.0%)	Minimally worse	1 (3.8%)	1 (5.0%)	2 (4.3%)	
Much worse	1 (0.6%)	3 (2.9%)	0 (%)	4 (1.5%)	Much worse	1 (3.8%)	1 (5.0%)	2 (4.3%)	
Very much worse	1 (0.6%)	1 (1.0%)	0 (%)	2 (0.7%)	Very much worse	1 (3.8%)	0 (0.0%)	1 (2.2%)	
Total	163 (100%)	103 (100%)	9 (100%)	275 (100%)	Total	26 (100%)	20 (100%)	46 (100%)	

CGI-E	EDS population				Total	CGI-E	Patella population		
	0-≤18 mo	>18 mo	Not known	Total			0-≤18 mo	>18 mo	Total
Very good	71 (44.4%)	34 (32.7%)	2 (22.2%)	107 (39.2%)	Very good	14 (53.8%)	6 (30.0%)	20 (43.5%)	
Moderate	55 (34.4%)	43 (41.3%)	4 (44.4%)	102 (37.4%)	Moderate	6 (23.1%)	7 (35.0%)	13 (28.3%)	
Slight	18 (11.2%)	13 (12.5%)	2 (22.2%)	33 (12.1%)	Slight	2 (7.7%)	5 (25.0%)	7 (15.2%)	
Unchanged or worse	16 (10.0%)	14 (13.5%)	1 (11.1%)	31 (11.3%)	Unchanged or worse	4 (15.4%)	2 (10.0%)	6 (13.0%)	
Total	160 (100%)	104 (100%)	9 (100%)	273 (100%)	Total	26 (100%)	20 (100%)	46 (100%)	

Note: The date of assessment was not available for all patients, and therefore, some assessments could not be categorized into short term (0-18 months) or long term (>18 months). All differences are not significant. EDS = Efficacy Data Set.

Effectiveness

Overall, ChondroCelect implantation resulted in a therapeutic effect (some degree of improvement that is considered to be related to the intervention only) in 242 (88.6%) of the 273 patients for whom a CGI-E assessment was obtained, while 11.3% (31/273) of patients were reported as “unchanged or worse”. Similarly, 238 (86.5%) of the 275 patients for whom a CGI-I assessment was obtained were reported to have improved after ChondroCelect implantation ($P = 0.52$), and 191 (69.5%) of 275 had improved much or very much. Similar ratios of patients who had much or very much improved were reported in those with short-term (0-≤18 months: 115/163 or 70.6%) versus long-term follow-up (>18 months: 70/103 or 68.0%) ($P = 0.68$). A very good or moderate therapeutic effect (CGI-E) was reported, overall, in 209 of 273 or 76.5%, with comparable rates in patients with short-term follow-up (126/160 or 78.8%) and patients with longer term follow-up (77/104 or 74.0%) ($P = 0.38$) (Table 3).

In patients with a patellar lesion, 40 (87.0%) of the 46 patients were reported to have an improved CGI-I after ChondroCelect implantation, which is identical to the number

(%) of patients having yielded a therapeutic effect (CGI-E) (Table 3). Similar rates of patients who had much or very much improved were obtained in those who were assessed in the short (0-≤18 months: 16/26 or 61.6%) versus the long term (>18 months: 12/20 or 60.0%) ($P = 1.00$). Overall, a similar rate of improvement, therapeutic effect, or worsening was observed in patients with a patellar lesion compared to the EDS population with, for example, 13% of patients (6/46) with a patellar lesion implanted with ChondroCelect reported as “unchanged or worse” ($P = 0.08$ v. 31/273 for EDS). A very good or moderate therapeutic effect (CGI-E) was reported, overall, in 33 of 46 or 71.7% ($P = 0.46$ v. 206/273 for EDS) (Table 3).

In patients with a lesion larger than 4 cm², 47 of 49 (95.1%) were reported to have an improved CGI-I after ChondroCelect implantation versus 137 of 164 (83.5%) patients with a smaller lesion (≤4 cm²) ($P = 0.38$) (Table 4). The CGI-I was rated “much” or “very much” improved in 37 of 49 (75.5%) and 111 of 164 (67.7%) patients with a larger and smaller lesion, respectively ($P = 0.38$), and the CGI-E was rated “moderate” to “very good” in 80.0% and 75.7% of patients with a larger lesion and smaller lesion, respectively ($P = 0.70$). Overall, in 4% to 6% of patients

Table 4. Clinical Global Impression–Improvement (CGI-I) and –Efficacy (CGI-E) According to Lesion Size Category

CGI-I	≤4 cm ²	>4 cm ²	Total	CGI-I	Single	Multiple	Total
Very much improved	47 (28.7%)	14 (28.6%)	61 (28.6%)	Very much improved	76 (31.9%)	6 (13.6%)	82 (29.1%)
Much improved	64 (39.0%)	23 (46.9%)	87 (40.8%)	Much improved	86 (36.1%)	23 (52.3%)	109 (38.7%)
Minimally improved	26 (15.9%)	10 (20.4%)	36 (16.9%)	Minimally improved	42 (17.6%)	5 (11.4%)	47 (16.7%)
No change	17 (10.4%)	1 (2.0%)	18 (8.5%)	No change	15 (6.3%)	5 (11.4%)	20 (7.1%)
Minimally worse	8 (4.9%)	1 (2.0%)	9 (4.2%)	Minimally worse	6 (2.5%)	5 (11.4%)	11 (3.9%)
Much worse	2 (1.2%)	0 (0.0%)	2 (0.9%)	Much worse	4 (1.7%)	0 (0.0%)	4 (1.4%)
Very much worse	0 (0.0%)	0 (0.0%)	0 (0.0%)	Very much worse	2 (0.8%)	0 (0.0%)	2 (0.7%)
Total	164 (100%)	49 (100%)	213 (100%)	Total	231 (100%)	44 (100%)	275 (100%)
CGI-E	≤4 cm ²	>4 cm ²	Total	CGI-E	Single	Multiple	Total
Very good	59 (36.6%)	19 (38.0%)	78 (37.0%)	Very good	95 (39.9%)	12 (27.3%)	107 (37.9%)
Moderate	63 (39.1%)	21 (42.0%)	84 (39.8%)	Moderate	84 (36.2%)	18 (40.9%)	102 (36.2%)
Slight	19 (11.8%)	7 (14.0%)	26 (12.3%)	Slight	27 (11.7%)	6 (13.6%)	33 (11.7%)
Unchanged or worse	20 (12.4%)	3 (6.0%)	23 (10.9%)	Unchanged or worse	23 (11%)	8 (18.4%)	31 (11%)
Total	161 (100%)	50 (100%)	211 (100%)	Total	229 (100%)	44 (100%)	273 (100%)

Note: All differences are not significant, except for CGI-I rate worse to no change (grouped): 16.5% (≤4 cm²) versus 4.1% (>4 cm²) ($P = 0.03$).

with a larger lesion, treatment with ChondroCelect did not provide any improvement (*status quo* or worse) versus 12% to 16% of patients with a smaller lesion (not significant) (Table 4).

In patients with single lesions, 204 of 231 (85.7%) were reported to have improved versus 10 of 44 (22.7%) in multiple lesions ($P = 0.056$) on CGI-I. The CGI-I was rated “much” or “very much” improved in 162 of 231 (68.7%) and 29 of 44 (65.9%) in patients with single and multiple lesions ($P = 0.36$). The CGI-E was rated “moderate” to “very good” in 179 of 229 (75.2%) and 30 of 44 (68.2%) in patients with single and multiple lesions ($P = 0.17$) (Table 4).

Safety

In 179 (53.6%) of 334 patients in whom AEs were reported, no clinically relevant, knee-related AE was reported. The most commonly reported AEs were knee pain (23.8%), joint effusion (8.5%), joint swelling (8.2%), joint crepitation (6.1%), muscle atrophy (6.1%), and decreased joint range of motion (5.7%) (Table 5). Of the AEs reported, 74.4% (233/313) were considered unlikely related or unrelated to ChondroCelect, and 77.6% (243/313) of the AEs were of mild or moderate intensity. In 62.0% (178/287), the reported AE was considered to be related to surgery. Twenty-four SAEs were reported to have occurred in 20 (6%) patients. Seven of these concerned arthrofibrosis of the involved knee (5 patellar lesions, and 2 medial femoral condyle lesions) and required manipulation under anesthesia. Three SAEs were reported as possibly related to ChondroCelect and related to the surgery (1 joint range of

Table 5. Adverse Events

Adverse events reported in ≥2% of patients	% of patients
Knee pain	23.8
Joint effusion	8.6
Joint swelling	8.2
Joint crepitation	6.1
Muscle atrophy	6.1
Joint range of motion decreased	5.7
Tendon disorder	3.9
Joint lock	3.2
Therapeutic product ineffective	3.2
Bone swelling	2.9
Joint instability	2.9
Synovitis	2.9
Arthrofibrosis	2.5
Cartilage hypertrophy	2.1

motion decreased, and 2 therapeutic product ineffective). The other SAEs were considered unlikely or not related to the study product. Half of the reports of “decreased joint range of motion” ($n = 8/16$) and the majority of AEs of “arthrofibrosis” ($n = 5/7$) were reported in patients with a patellar lesion (8/84 v. 8/250, $P = 0.03$; and 5/84 v. 2/250, $P = 0.01$). Nine of 18 reports of joint crepitation were considered to be related to ChondroCelect. Nine of 18 reports of joint crepitation occurred in patients treated for a patellar lesion (9/84 v. 9/250, $P = 0.02$). Cartilage hypertrophy was reported, overall, in 6 of 334 (2.1%) patients and none in patellar lesions (not significant). There was no difference in occurrence of AEs ($P = 0.6$) or SAEs ($P = 0.54$) between single and multiple lesions.

Discussion

Overall, looking at our data, articular cartilage repair with ChondroCelect appeared to be well tolerated and efficacious when implanted in an unselected heterogeneous population of patients suffering from symptomatic cartilage lesions. The demographics and locations of the lesions for patients in the CUP are comparable to those reported in previous reports,^{9,13-18} and the studied population thus appears to be representative of the population of patients with symptomatic cartilage lesions encountered in daily clinical practice. ChondroCelect implantation in this group of compassionate use patients resulted, overall, in a therapeutic improvement in 89% of patients as assessed using the CGI-E, and similar rates were observed in those with a patellar lesion (87%). Contrary to what has been reported in the literature concerning the lack of applicability of clinical results from an RCT,⁶ this study shows that even in a variable daily clinical practice group of patients, similar results can be obtained.

In an RCT with the same product by Saris *et al.*, the ratios of patients having improved from baseline based on the Knee injury and Osteoarthritis Outcome Score (KOOS) and visual analog scale (VAS) for pain assessment were 82% and 78%, respectively, at 24 months and 83% (KOOS and VAS) at 36 months.⁵ While it is not unusual to have better scores from investigator-rated global assessments, the CGI outcome scores in this study are very comparable to patient-rated outcome assessments like the KOOS and VAS and the Lysholm score in other studies on ACI,¹⁹⁻²¹ where results are reported between 70% and 85% depending on lesion site.

The AEs reported were consistent with those expected in patients undergoing knee surgery and chondrocyte implantation. There was a difference though in the rate of cartilage hypertrophy seen with only 2.1% in this group compared to other literature reporting up to 50% of reinterventions for this reason.^{9,22,23} Wood *et al.*, in an article on reported safety issues to the US Food and Drug Administration (FDA) after ACI, described similar issues of graft delaminations (22%), tissue hypertrophy (17%), chondromalacia (12%), arthrofibrosis (5%), and “other mechanical symptoms” (23%).²³ The AEs reported give no indication of a significant safety issue or risk that would suggest that the ChondroCelect procedure is unwarranted in the patient population studied. Peterson *et al.*, in his long-term data, did not specifically cover the topic on safety but showed that good and consistent results can be obtained in very different groups of patients at more than 10 years’ follow-up.²⁴ Vasiliadis *et al.* described 29% periosteal hypertrophy in a group of 92 patients with cartilage repair in the patellofemoral joint.²⁵ It also appears that the observed positive benefit/risk balance of ChondroCelect implantation is maintained in the long term.²⁴

From our observations, it further appears that patients with a patellar lesion undergoing treatment with ChondroCelect may be more prone to developing arthrofibrosis (5 patellar v. 2 femoral lesions), decreased joint range of motion, and joint crepitations. One probable cause could be the range of motion restrictions during the first 4 to 6 weeks to prevent early shear and loosening of the graft. In a recent article by Vasiliadis *et al.* on patellofemoral ACI with periosteum in a group of 92 patients, they experienced that 8% of patients developed arthrofibrosis requiring surgical release.²⁵ Gobbi *et al.*, on the other hand, using a second-generation technique with arthroscopic implantation of chondrocytes on a scaffold, only reported 2 patients in their group of 34 showing only 1 graft hypertrophy.²⁶ The expected benefit from implanting ChondroCelect in a patellar lesion does not appear to significantly differ from the benefit of using it in patients with femoral cartilage lesions in our patient group. The overall benefit/risk balance of implanting ChondroCelect in patellar lesions therefore appears to be positive as well.

The weakness of this study is its cross-sectional design, the absence of a control treatment, the absence of patient-reported outcome measures, the large heterogeneity of the participants and lesions, a single product that is discussed, and the validity of the CGI score that has only been validated in psychiatry and not in orthopedics.

In conclusion, however, the large number of patients observed in a pragmatic study design and the overall high response rate (90.3%) provide interesting and valuable data that are complementary to the data from well-controlled studies performed with ChondroCelect and indicate that the overall positive benefit/risk balance yielded by ChondroCelect in a well-controlled but selected study population can be extended to the larger situation of everyday clinical practice.

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