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Autologous Chondrocyte Implantation: Scaffold-Based Solutions

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Abstract

Autologous chondrocyte implantation is a surgical technique utilized for repair of articular cartilage defects. The originally described technique for autologous chondrocyte implantation involves applying a liquid suspension of the cultured chondrocytes to a cartilage defect and sealing the defect with a periosteum or collagen patch. Scaffolds for housing chondrocytes were introduced to allow for increased ease of delivery and application, to avoid leakage of chondrocytes out of the defect, and to allow for an implant that more closely mimics the non-uniform tissue architecture of healthy articular cartilage. In this chapter we describe the design, clinical outcomes, and commercial availability of various scaffolds reported in the clinical literature for autologous chondrocyte implantation.

Keywords: scaffold, MACI, MACT, autologous chondrocyte implantation, 3rd generation ACI

1. Introduction

Autologous chondrocyte implantation (ACI) is a two-stage articular cartilage repair technique for treatment of articular cartilage defects. Originally described by Brittberg et al. [1], it involves an initial surgery to harvest chondrocytes from a non-weight bearing portion of the distal femur, typically the intercondylar notch or medial or lateral margin of the trochlea. The cartilage extracellular matrix is then enzymatically digested within the laboratory to isolate the chondrocytes. The harvested chondrocytes are then cultured in a laboratory. In the second stage, a liquid suspension of chondrocytes is applied to the cartilage defect and is sealed in place with a soft tissue membrane cover [1]. Originally periosteum was utilized as the cover, though a collagen membrane was later introduced to minimize periosteal donor site morbidity and risk of periosteal

patch hypertrophy [2]. Disadvantages of ACI with periosteum or collagen membrane covers with the use of a liquid cultured chondrocyte suspension include a high degree of technical difficulty, potential for leakage of chondrocytes, and non-uniform distribution of chondrocytes.

Scaffolds for housing chondrocytes were introduced for increased ease of delivery and application, to avoid leakage of chondrocytes out of the defect, and to allow homogeneous distribution of chondrocytes within the defect [3]. Additionally, there is some evidence that chondrocytes grown in monolayer culture do not fully regain their original phenotype [3, 4], which has prompted research in culture directly within a scaffold and design of implants that more closely mimics the non-uniform tissue architecture of healthy articular cartilage [3]. Use of a 3-dimensional structure for chondrocyte culture has been shown to maintain the chondrocyte differentiated phenotype [5]. Use of a scaffold is termed 'matrix-assisted autologous chondrocyte transplantation,' or the MACT procedure, and has been employed in clinical practice in Europe since 1998. The MACT procedure involves implantation of a chondrocyte seeded biocompatible scaffold in the articular defect [2]. The implant is fixed in place with fibrin glue with no membrane cover and allows for implantation with use of a mini-arthrotomy or arthroscopic implantation. The field of scaffold-based ACI has greatly expanded in recent years, with more than a dozen implants developed (**Table 1**). A wide variety of natural and synthetic materials have been utilized in MACT scaffolds; though clinical outcomes studies are generally favorable regardless of scaffold design, the number of published studies and length of follow-up vary widely among implants.

In this chapter, the design rationale, commercial availability, and clinical results of various scaffolds for use in MACT will be described. Of note, all implants described in this chapter follow a two-step implantation protocol (initial cartilage harvest and culturing of chondrocytes followed by a delayed implantation several weeks later). The single-stage implantation techniques with published outcomes data are either no longer commercially available (the CAIS implant) [6], or have yet to be marketed [7].

| Scaffold content | Commercial name | Implantation steps |
|---|-----------------------------|--------------------|
| Porcine collagen I/III membrane | MACI | Two-steps |
| Three-dimensional collagen I based scaffold | NeoCart | Two-steps |
| Three-dimensional collagen I based scaffold | CaReS | Two-steps |
| Three-dimensional collagen I based scaffold | Novocart 3D | Two-steps |
| Hyaluronic acid based scaffold | Hyalograft C | Two-steps |
| Human fibrin and recombinant hyaluronic acid-based scaffold | BioCart II | Two-steps |
| Fibrin based gel | Chondron | Two-steps |
| Hydrogel of agarose and alginate | Cartipatch | Two-steps |
| Atelocollagen gel | Koken Atelocollagen Implant | Two-steps |
| Fibrin, polyglycolic/polylactic acid, polydioxanone | BioSeed-C | Two-steps |

Table 1. Summary of MACT scaffolds.

2. Scaffolds utilized for autologous chondrocyte implantation

2.1. Porcine collagen I/III membranes

2.1.1. MACI

As of December 2016, matrix-assisted chondrocyte implantation (MACI; Vericel, Cambridge, MA) is currently the only FDA approved MACT technique for use in the United States. In this technique, chondrocytes are cultured ex-vivo in a monolayer and then seeded on one side of a porcine collagen I/III membrane (**Table 2**). At the second stage operation (re-implantation), the side seeded with chondrocytes (the roughened side) is placed against the subchondral bone surface and the graft is secured with fibrin glue [8]. The implantation may be performed arthroscopically or with a mini-arthrotomy, and recent work demonstrates MACI grafts may be safely applied with use of carbon dioxide insufflation arthroscopy [9]. Regardless of technique, gentle handling of the graft is recommended, as excessive or forceful handling of the graft causes a significant decrease in viable chondrocytes [10]. A histologic study of 56 MACI patients up to 6 months after surgery demonstrated that chondrocytes appeared well-integrated and maintained chondrocyte phenotype [11]. Hyaline-like cartilage production began as early as 21 days after implantation, and there was 75% hyaline-like cartilage regeneration at 6 months [11]. Another histologic study of 33 second-look biopsies at median 15 months after surgery found a median ICRS histological grade of 57 which did not correlate with an arthroscopic ICRS grade of normal in 30% of cases and nearly normal in 51% of cases [12].

Several comparative studies have been performed with MACI, all of which demonstrated encouraging results (**Table 3**). However, it should be noted that use of MACI in clinical practice tends to be in larger defects (mean 5.64 cm²) than lesions treated in clinical trials (weighted mean 4.89 cm²) [13]. Approval by the FDA was based primarily on results of the SUMMIT trial, reported by Saris et al. [14]. In this randomized trial, 144 patients with high grade femoral condylar defects were randomized to MACI or microfracture and followed for 2 years; mean defect size was equivalent between groups (4.9 cm² MACI vs. 4.7 cm² microfracture) [14]. At final follow-up there was significantly better improvement in KOOS symptom scores with MACI, lower failure rates, yet no difference in repair quality as assessed by histology or MRI versus microfracture [14]. A randomized controlled trial was performed by Bartlett et al. with comparison of ACI-C (ACI with collagen cover) and MACI for treatment

| Commercial name | Manufacturer | Structure | Expansion | Availability |
|-----------------|--|--|---|--|
| MACI | Vericel, Cambridge, MA (Formerly provided by Verigen Transplantation Service, Copenhagen, Denmark) | Porcine-derived collagen I/III bilayer | Cells are expanded in monolayer then seeded onto porous side of collagen membrane | FDA approved for use in the USA. Available in Europe and Australia |

FDA, U.S. Food and Drug Administration.

Table 2. MACT with porcine collagen I/III membrane scaffold.

| Level of evidence | Author | Implant and sample size | Mean follow-up | Outcome |
|-------------------|-----------------------|---|----------------|--|
| 1 | Ebert et al. [20] | 19 MACI-standard WB; 18 MACI-accelerated WB | 2 years | Randomized trial of standard 8 week return to weight bearing versus accelerated 6 week return to weight bearing. No difference in symptom improvement. |
| 1 | Wondrasch et al. [21] | 15 MACI-standard WB; 16 MACI-accelerate WB | 5 years | Randomized trial of 6 versus 10 week return to weight bearing. No difference in symptom improvement between groups. MOCART score decreased from years 2 to 5 which did not correlate with symptom scores |
| 1 | Akgun et al. [18] | 7 MACI; seven mesenchymal stem cell | 2 years | Small randomized trial of MACI versus stem cells (also seeded onto a collagen scaffold. Stem cell group had greater symptom improvement at 6 months but similar improvement at final follow-up. |
| 1 | Basad et al. [15] | 40 MACI; 20 microfracture | 2 years | At 24 months, greater improvements seen with MACI in Tegner activity score, subjective symptoms scores and ICRS scores on 2nd look arthroscopy. |
| 1 | Saris et al. [14] | 72 MACI; 72 microfracture | 2 years | Greater improvement in KOOS scores, lower failure rate with MACI (12.5%) versus microfracture (31.9%). Similar MRI and histologic outcomes. |

Table 3. Outcomes of MACT with collagen I/III membrane scaffold (MACI) from level 1 prospective clinical studies.

of high grade chondral defects. Mean defect size was 6.0 cm² for the MACI group and 6.1 cm² for the ACI-C group [8]. At 1 year follow-up both groups demonstrated significant improvement in Cincinnati knee scores and similar re-operation rates (9% for both groups) [8]. Basad et al. performed a randomized study of MACI versus microfracture with 2 years follow-up on high grade defects 4–10 cm² [15]. The MACI group in this study had greater improvements in symptom scores, activity scores, and ICRS surgeon grading of cartilage appearance at second look arthroscopy [15]. In a comparative imaging and clinical study of MACI versus osteochondral autograft transfer (OAT) by Salzman et al., superior Lysholm symptoms scores were observed in the MACI group; patients in this study were matched for demographics, but MACI-treated lesions were >3 cm² and OAT-treated lesions were <3 cm² [16]. For treatment of chondromalacia patella, Macmull et al. noted a higher rate of good-excellent patient symptom scores with MACI (56.5%) than ACI-C (40%). Higher rates of clinical failure (poor patient-rated symptoms) were noted with lateral facet lesions, and the authors did not report distribution of lesions (medial facet, lateral facet, or multiple facets) by treatment group [17]. Finally, Akgun et al. report a small randomized trial of MACI versus autologous mesenchymal stem cells (also seeded onto a collagen scaffold) with 2 years follow-up [18]. The stem cell group had greater symptom improvement at 6 months but similar improvement at final follow-up; no clinical failures were noted in either group [18].

Several randomized trials of delayed versus accelerated weight-bearing after MACI have been performed (**Table 3**). A randomized trial of 6 week versus 8 week return to full weight bearing found no significant difference in failure rates or symptom improvement at 2 years (interim 12-month results reported in an earlier publication [19]); the study authors concluded accelerated weight bearing after MACI is safe [20]. Another trial of 6 week versus 10 week return to full weight bearing with 5 years follow-up after MACI similarly found no difference in symptom improvement between groups [21]. The authors note that MRI-based MOCART scores decreased from years 2 to 5 but did not correlate with symptom scores [21].

Several case series have reported also reported good results with MACI (**Table 3**). The series with the longest follow-up is reported by Gille et al.; of 19 cases with mean 16 years follow-up, 21% underwent knee arthroplasty (4/19), with durable symptom improvement in the remaining 15 patients [22]. In another series of MACI patients, Basad et al. report durable improvements in activity and symptoms scores and a failure rate of 18.5% at 5 years with MACI [23]. Behrens et al. similarly report 8/11 patients rated their current knee function as 'much better or better' than their pre-operative function at 5 years follow-up [24]. A larger case series by Ebert et al. of 41 patients and 5 years follow up (35/41, 85% with 5 years follow-up) reported significant improvements in knee function, a 12% rate of graft hypertrophy at 5 years, and a graft failure rate of 3% at 5 years [25]. Durable results are seen with arthroscopic implantation of MACI scaffolds, as Ebert et al. report stable clinical improvement at 5 years follow-up and a failure rate of 6.4% [26]. Ventura et al. note improvement in Lysholm symptom scores at 2 years but no change in Tegner activity scores in a series of 53 patients; a high rates of subchondral abnormalities were noted on MRI at 1 year (70% of cases) which did not correlate with clinical symptoms [27].

For the patellofemoral joint, Meyerkort et al. report durable improvement in symptoms at 5 years with MACI; clinical improvement did not correlate with MRI assessment of graft appearance at 5 years [28]. Gigante et al. published results of treatment of patellar defects with MACI and concomitant distal realignment; at 3 years, there was significant improvement in symptoms in most patients and one clinical failure (7%) [29].

As a salvage operation in young patients with medial compartment osteoarthritis, Bauer et al. report significant clinical improvement at 5 years with combined high tibial osteotomy and MACI; however, they note declining results and high graft failure over time for this salvage operation [30]. Finally, outcomes for MACI and concomitant bone grafting for treatment of osteochondral lesions with use of a bilayer 'sandwich' technique have also been reported. Vijayan et al. report outcomes with use of two MACI membranes and impaction bone grafting of osteochondral lesions greater than 8 mm depth; at a mean 5.2 year's follow-up, 12/14 patients had good to excellent results with one graft failure [31].

2.2. Three-dimensional collagen I based scaffolds

2.2.1. NeoCart

NeoCart (Histogenics Corporation, Waltham, Massachusetts) is an MACT implant that consists of a three-dimensional bovine collagen I scaffold (**Table 4**). Rather than being cultured

| Commercial name | Manufacturer | Structure | Expansion | Availability |
|-----------------|--|---------------------------------------|--|--|
| NeoCart | Histogenics Corporation, Waltham, Massachusetts | Bovine collagen type I matrix | Cells are expanded directly on 3D scaffold via a custom bioreactor | Ongoing phase III clinical trials; not yet approved by the FDA |
| CaReS | Arthro Kinetics (Ars Arthro, Esslingen, Germany) | Rat collagen type I matrix | Cells are mixed with collagen which forms a gel and cultured for 2 weeks | SFDA certified; not yet approved by the FDA |
| Novocart 3D | B. Braun-Tetec, Reutlingen, Germany | Collagen-chondroitin sulfate scaffold | Initial monolayer culture followed by seeding onto scaffold; re-implantation 3–4 weeks after harvest | Available in Europe, ongoing phase III clinical trials. |

FDA, U.S. Food and Drug Administration; SFDA, State Food and Drug Administration of China; 3D, three-dimensional.

Table 4. MACT with three-dimensional collagen 1 scaffold.

in a monolayer, the scaffold is seeded initially with chondrocytes which then proliferate in a custom bioreactor [32]. The bioreactor is designed to incubate the scaffold in a low-oxygen tension environment with varying pressure to mimic the native intra-articular environment with the goal of preserving the chondrocyte phenotype [33]. At the time of implantation, the graft is fixed to the defect with a proprietary adhesive (CT3 bioadhesive, Histogenics). A randomized phase II trial by Crawford et al. of distal femoral lesions treated with NeoCart versus microfracture demonstrated superior improvement in IKDC and KOOS scores at 24 months with NeoCart and no difference in adverse events between groups (**Table 5**) [33]. A small case series (8 patients) with 2 years follow-up demonstrated significant symptom improvement from baseline and no cases of graft hypertrophy or arthrofibrosis (**Table 5**) [32]. Defect fill was noted to be moderate (33–66%) in 1/8 cases and poor (<33%) in 1/8 cases. A longitudinal

| Level of evidence | Author | Implant and sample size | Mean follow-up | Outcome |
|-------------------|----------------------|-----------------------------|----------------|--|
| 1 | Crawford et al. [33] | 21 NeoCart; 9 microfracture | 2 years | Randomized trial of distal femoral lesions. Greater IKDC and KOOS improvement at 2 years with NeoCart. |
| 3 | Flohe et al. [35] | 9 CaReS; 11 MACI | 1 year | No difference in clinical outcomes between groups. |
| 3 | Petri et al. [36] | 17CaReS; 10 microfracture | 3 years | Comparative trial for patellofemoral defects. No difference in groups between IKDC, SF-36, or Cincinnati knee scores at 3 years follow-up. |

Table 5. MACT clinical outcome studies with three-dimensional collagen 1 scaffold.

clinical and MRI-based study with 5 years follow-up by Anderson et al. demonstrate that clinical improvement and graft appearance on MRI both evolve over the first 24 months after surgery [34]. Both clinical scores and MRI appearance appeared stable from 24 to 60 months follow-up [34].

2.2.2. *CaReS*

The Cartilage Regeneration System (CaReS, Ars Arthro, Esslingen, Germany) utilizes a rat-derived collagen I gel rather than the bovine collagen matrix utilized by NeoCart (**Table 4**). The harvested chondrocytes are similarly seeded into the collagen gel and cultured in this 3-dimensional environment with the intention of preserving cartilage phenotype. In a small comparative study of CaReS (9 patients) versus MACI (11 patients) with 1 year follow-up, Flohe et al. demonstrate significant improvement in symptoms with no difference between groups (**Table 5**) [35]. A small comparative study of microfracture (n = 10) vs. CaReS (n = 17) for patellofemoral lesions found significant improvements in symptoms from baseline with no difference in outcomes between groups [36]. In a multicenter clinical trial, Schneider et al. report outcomes of 116 at mean 30.6 month follow-up from 9 different centers; mean defect size in the trial was 5.4 cm² [37]. At final follow-up there was significant improvement in IKDC, VAS and SF-36 scores and a patient satisfaction rate of 80%. A total of 8 revision arthroscopies were performed for pain with 2 cases of implant hypertrophy and 2 cases of early failure [37]. In an imaging based outcome study, Welsch et al. compared 3T MRI results at 2 years for Hyalograft C versus CaReS and found greater T2 relaxation times for CaReS despite similar clinical outcomes between groups [38].

2.2.3. *Novocart 3D*

The Novocart 3D implant (B. Braun-Tetec, Reutlingen, Germany) is a collagen-chondroitin sulfate sponge (**Table 4**). After chondrocyte harvest, cells are initially cultured in a monolayer and then seeded onto the collagen-chondroitin sulfate scaffold at a density of 0.5–3.0 × 10⁶ cells/cm², after which the scaffold is cultivated in serum for 2 days before shipment for re-implantation [39]. Niethammer et al. performed several MRI-based studies of graft maturation and graft filling with Novocart 3D. In a 3 years prospective MRI study, graft maturation as assessed by T2 mapping required at least 1 year [40]. In a 2 years prospective MRI study, incomplete graft filling as assessed by MRI was common (55.7%) at 2 years and did not correlate with clinical results; the authors noted that graft thickness appeared to increase throughout the 2 years follow-up period [41]. A 2 years follow-up MRI study showed a 25% graft hypertrophy rate in Novocart 3D patients (11/44 patients), with higher hypertrophy rates in cases of acute traumatic defects or osteochondritis dissecans [42].

In a small non-randomized comparative study, Panagopoulos et al. report outcomes of Novocart 3D (n = 9) and ACI-P (periosteal cover) (n = 11) and mean 37.5 months follow-up (**Table 5**) [43]. No significant difference in Tegner, Lysholm, or IKDC scores was noted between groups. The patient population consisted of high demand athletes and soldiers, with low rates of return to pre-injury activity levels (6/19, 31.5%) [43]. In a comparative study of 40 pediatric (<20 years old) patients treated with Novocart 3D versus 40 matched adult historical controls who also

underwent Novocart for similar size/location lesions, both groups had significant improvement in VAS and IKDC scores at 36 months, but the pediatric group had greater improvement than the adult group at final follow-up [44]. A case series of 23 patients with 2 years follow-up by Zak et al. report improvement in symptoms scores as well as activity scores versus baseline with use of Novocart 3D [39]. At final follow-up, hypertrophy was noted via MRI in 16% and incomplete filling (>50%) in 20% of patients [39]. A large case series by Angele et al. of 433 patients with mean 6.9 months follow-up (max 2.5 years) found an 8.5% re-operation rate, a 6% graft failure rate in patients with >12 months follow-up [45]. Finally, in a case series with 2 years follow-up, Niethammer noted that clinical outcomes at 2 years were worse for patients who returned to sport/physical activities at earlier than 12 months after surgery [46].

2.3. Hyaluronic acid or fibrin based scaffolds

2.3.1. Hyalograft C

The Hyalograft C scaffold is based on the benzylic ester of hyaluronic acid (HYAFF 11; Fidia Advanced Biopolymers Laboratories, Padova, Italy) (Table 6). The resulting scaffold is a meshwork of 20 micrometer diameter fibers. The cells are cultured directly on the scaffold with resulting collagen II and aggrecan production [5]. The implant is naturally adhesive and does not require an additional adhesive at time of implantation. Clinical outcomes of Hyalograft C were encouraging, with superior results in comparison to microfracture [47] and comparable results to MACI [48] or traditional ACI with a periosteum cover (Table 7) [49]. However, production of this implant has been discontinued by the manufacturer in favor of further development of a single-stage delivery system (no published clinical outcomes data available for the single-stage system).

| Commercial name | Manufacturer | Structure | Expansion | Availability |
|-----------------|---|--|---|---|
| Hyalograft C | Anika Therapeutics (Fidia Advanced Biopolymers Laboratories, Padova, Italy) | Benzylic ester of hyaluronic acid (HYAFF) combined with expanded patient cells | Cells seeded and cultured directly on scaffold | No longer commercially available; production discontinued |
| BioCart II | Histogenics Corporation, Waltham, MA (merger with former supplier, ProChon Biotech) | Human fibrin and recombinant hyaluronic acid-based scaffold | Cells cultured in human serum and growth factor FGF2v1, then seeded onto scaffold | Available in Italy, Greece, and Israel; ongoing clinical trials in the United States; not yet approved by the FDA |
| Chondron | Sewon Cellontech, Seoul, Korea | Fibrin based gel | Cells cultured in serum; at time of surgery, suspension is mixed 1:1 with fibrin | Available in Korea |

AIFA, Italian Medicines Agency; FDA, U.S. Food and Drug Administration.

Table 6. Hyaluronic acid or fibrin-based scaffolds.

| Level of evidence | Author | Implant and sample size | Mean follow-up | Outcome |
|-------------------|----------------------|-----------------------------------|----------------|--|
| 2 | Kon et al. [47] | 21 Hyalograft C; 20 microfracture | 7.5 years | Return to sport was a median 8 months for microfracture, 12.5 months for Hyalograft C. Symptom improvement with microfracture deteriorated with time whereas Hyalograft C was durable. |
| 3 | Kon et al. [48] | 22 Hyalograft C; 39 MACI | 5 years | All patients 40 years or older, treated with mini-open MACI or arthroscopic Hyalograft C. Overall failure rate 20%, similar symptom improvement seen in both treatment groups. |
| 3 | Ferruzzi et al. [49] | 50 Hyalograft C; 48 ACI-P | 2–5 years | Similar IKDC improvement at 2+ years. Greater symptom improvement in first 12 months in Hyalograft C (arthroscopic) group versus ACI-P (mini-open) |

Table 7. MACT clinical outcome studies with hyaluronic acid or fibrin-based scaffolds.

2.3.2. BioCart II

An implant called BioCart II (Histogenics Corporation, Waltham, MA formerly supplied by ProChon Biotech prior to merger with Histogenics) is comprised of a scaffold of recombinant hyaluronan with fibrin to form a sponge (**Table 6**). Cells are initially cultured in human serum with recombinant fibroblast growth factor 2 variant (FGF2v1) and then seeded onto the scaffold prior to implantation with a mini-open approach. A small 1 year outcome study by Nehrer et al. of 8 patients demonstrated significant improvement in IKDC and Lysholm scores; 3 patients had a transient effusion post-operatively and there were no clinical failures (**Table 7**) [50]. A case series by Eshed et al. of patients who underwent MRI evaluation at mean 17.3 months after surgery (range 6–48 months) found continued maturation of cartilage with time (>1 year versus <1 year) and higher IKDC scores in patients with >12 months follow-up and without a history of prior cartilage surgeries [51].

2.3.3. Chondron

The Chondron scaffold is a fibrin-based gel (Sewon Cellontech Co. Ltd., Seoul, Korea) (**Table 6**). Chondrocytes are first cultured separately in a specialized serum (CRM kit, Sewon Cellontech, Korea). At the time of surgery the serum and cultured chondrocytes are mixed 1:1 with fibrin and injected directly onto the defect. In addition to typical preparation of the defect for ACI, several holes are drilled into the subchondral bone to improve adherence [52]. Choi et al. report a multicenter study of 98 patients with mean 24 month follow-up treated with Chondron (**Table 7**) [52]. Symptom improvement increased with time, with greater improvement noted with >25 months follow-up versus <25 months. Complication rates were low with one early repeat operation (1%) and two cases of symptomatic catching (2%) [52]. Similar findings were reported in a series by Kim et al., with no graft-related complications among 30 patients at 24 months follow up; a second look arthroscopy at 12 months showed nearly normal cartilage

in 8/10 patients [53]. A small series by Konst et al. of 9 patients with osteochondral defects (mean depth 0.9 cm) treated with autologous bone grafting as well as Chondron showed satisfactory short term results at 12 months; there was one treatment failure which was converted to a unicompartmental knee arthroplasty [54].

2.4. Alginate based scaffolds

2.4.1. Cartipatch

Cartipatch (TBF Tissue Engineering, Mions, France) is a MACT implant with a scaffold composed of agarose and alginate (**Table 8**). Chondrocytes are first cultured in a monolayer and then mixed with a hydrogel of agarose and alginate. The hydrogel can be manipulated at 37°C and will solidify around 25°C, allowing formation of complex/irregular shapes with the scaffold. A multicenter randomized trial with 2 years follow-up was recently published by Clave et al. (**Table 9**) [55]. In this study, 30 patients were randomized to Cartipatch and 25 to mosaicplasty; all patients had isolated high grade femoral condylar defects 2.5–7.5 cm² in size. At 2 years, there was significantly greater improvement in IKDC scores with mosaicplasty than Cartipatch, though both groups had significant improvement over baseline. A total of 12 adverse events were reported for the Cartipatch groups and six in the mosaicplasty group [55]. An earlier case series by Selmi et al. reported 2 years outcomes of 17 patients treated with Cartipatch with a mean defect size of 3 cm² [56]. All patients had significant symptom improvement with no clinical failures; second look biopsies in 13 patients had mostly hyaline-like cartilage in 62% of cases (8/13) [56].

| Commercial name | Manufacturer | Structure | Expansion | Availability |
|-----------------|---|--|--|--|
| Cartipatch | Tissue Bank of France (TBF) Tissue Engineering, Mions, France | Alginate-agarose hydrogel combined with autologous cells | Two-step procedure; reduces cell leakage and implantation time | Ongoing phase III clinical trials; not yet approved by the FDA |

FDA, U.S. Food and Drug Administration.

Table 8. Alginate hydrogel.

| Level of evidence | Author | Implant and sample size | Mean follow-up | Outcome |
|-------------------|-------------------|--------------------------------|----------------|--|
| 1 | Clave et al. [55] | 30 Cartipatch; 25 mosaicplasty | 2 years | Both groups showed improvement in IKDC scores over baseline though mosaicplasty had greater symptom improvement than Cartipatch at 2 years for femoral lesions 2.5–7.5 cm ² . |
| 4 | Selmi et al. [56] | 17 Cartipatch | 2 years | Multicenter study. Significant symptom improvement in all patients, no clinical failures. Second look biopsies showed mostly hyaline-like cartilage in 8/13 patients (62%). |

Table 9. MACT clinical outcome studies with alginate-based scaffolds.

2.5. Atelocollagen gel

2.5.1. Koken Atelocollagen Implant

The MACT technique with use of the Koken Atelocollagen Implant (Koken, Tokyo, Japan) is similar to the ACI-P (periosteum cover) technique, but chondrocytes are suspended in atelocollagen gel rather than a liquid to obtain uniform distribution of chondrocytes within the defect and theoretically reduce risk of leakage (**Table 10**). In this technique, after initial isolation of chondrocytes from cartilage biopsy, the chondrocyte suspension is mixed 1:4 with a 3% bovine atelocollagen solution (Koken, Tokyo, Japan) [57]. Chondrocytes are expanded in this mixture for 28 days; the final product (the Koken Atelocollagen Implant) is an opaque implant with a jelly-like consistency. The Koken Atelocollagen Implant is implanted with a mini-arthrotomy and requires a periosteum cover to contain the atelocollagen-based scaffold within the defect [57]. A multicenter trial in Japan reported by Tohyama et al. reports use of the Koken Atelocollagen Implant and periosteum cover in 27 patients (**Table 11**) [57]. Overall there was a significant improvement in Lysholm scores at final 2 years follow-up. On second look arthroscopy, 24% of repair sites were ICRS grade normal and 48% were nearly normal. There was one case of graft hypertrophy, two cases of graft detachment, and two cases of abnormal or severely normal ICRS grade on second look arthroscopy [57]. Recently, Tadenuma et al. report clinical and imaging outcomes of 8 patients (11 knees) at mean 5.9 years after surgery [58]. The authors note significant improvement in Lysholm scores over baseline with one clinical failure (9%) and one traumatic repeat injury 7 years after surgery (9%). The authors report a correlation between T1 values of the repair site on MRI and clinical outcomes but no correlation between T2 values and outcomes [58].

| Commercial name | Manufacturer | Structure | Expansion | Availability |
|-----------------------------|---------------------|---|--|--------------------|
| Koken Atelocollagen Implant | Koken, Tokyo, Japan | Atelocollagen gel (3% type 1 bovine collagen gel) | Chondrocyte suspension is initially mixed 1:4 with 3% atelocollagen solution. The mixture is cultured for 4 weeks and thickens to a jelly-like consistency over that time. | Available in Japan |

Table 10. Atelocollagen based scaffold.

| Level of evidence | Author | Implant and sample size | Mean follow-up | Outcome |
|-------------------|----------------------|--------------------------------|----------------|---|
| 4 | Tohyama et al. [57] | 27 Koken Atelocollagen Implant | 2 years | Multicenter study. Symptom scores (Lysholm) improved at 2 years from baseline. Two cases of graft detachment (7.4%). Two remaining cases were graded abnormal or severely abnormal on second look arthroscopy (8%, 2/25). |
| 4 | Tadenuma et al. [58] | 11 Koken Atelocollagen Implant | 5.9 years | Improved Lysholm scores at final follow-up with one clinical failure (9%). T1 scores on MRI at final follow-up correlated with clinical scores but T2 scores did not. |

Table 11. MACT clinical outcome studies with alginate-based scaffolds.

2.6. Polyglycolic/polylactic acid and polydioxanone based scaffold

2.6.1. BioSeed-C

The BioSeed-C (BioTissue Technologies GmbH, Freiburg, Germany) MACT scaffold is comprised polyglycolic/polylactic acid (polyglactin, vicryl), and polydioxanone (**Table 12**). Harvested chondrocytes are first expanded in serum and then seeded into the polymer scaffold with fixation by fibrin. The scaffold is available in a standard rectangular shape (2 cm × 3 cm × 0.2 cm thickness) can be implanted arthroscopically or with a mini-arthrotomy. The defect must be contoured to a rectangular shape (more than one scaffold can be used as needed for larger defects) and corners of the scaffold are secured with transosseous resorbable suture loops [59].

In a comparative non-randomized study of ACI-P versus BioSeed-C with minimum 2 years follow up, Erggelet et al. report similar improvement in symptom scores (**Table 13**) [60]. The graft failure rate was similar between groups (3/42 ACI-P; 2/40 BioSeed-C), but re-operation rates were twice as high in the ACI-P group, primarily due to graft hypertrophy [60]. A smaller randomized study of ACI-P (n = 10) versus BioSeed-C (n = 9) with 2 years follow-up by Zeifang et al. found similar improvement in symptoms between groups (per IKDC score) at both 1 and 2 years [61]. In contrast to the findings reported by Erggelet et al. [60], re-operation rates were higher in the BioSeed C group (3/11 patients) versus ACI-P (1/10 patients) [61].

| Commercial name | Manufacturer | Structure | Expansion | Availability |
|-----------------|--|---|--|--|
| BioSeed-C | BioTissue AG (BioTissue Technologies, GmbH, Freiburg, Germany) | Fibrin, polyglycolic/polylactic acid and polydioxanone-based material combined with culture-expanded autologous chondrocytes and suspended in fibrin. | Chondrocytes cultured in serum then subsequently seeded into scaffold. | CE mark approval; not yet approved by the FDA. |

CE, Conformité Européenne; FDA, U.S. Food and Drug Administration.

Table 12. Scaffolds with polyglycolic/polylactic acid and polydioxanone.

| Level of evidence | Author | Implant and sample size | Mean follow-up | Outcome |
|-------------------|----------------------|-------------------------|------------------------------|---|
| 2 | Zeifang et al. [61] | 11 BioSeed-C; 9 ACI-P | 2 years | Similar IKDC symptom improvement in both groups at 1 year and 2 years. Higher re-operation rate in BioSeed C group. |
| 3 | Erggelet et al. [60] | 40 BioSeed-C; 42 ACI-P | 36 m ACI-P 24 m BioSeed-C | Twice as many re-operations required for ACI-P versus BioSeed-C. Three graft failures in ACI-P group and two in BioSeed-C group. Equivalent improvement in symptom scores between groups. |

Table 13. MACT clinical outcome studies with polyglycolic/polylactic acid and polydioxanone based scaffold.

Several case series have also been reported for BioSeed-C (**Table 13**). Ossendorf et al. report a case series of 40 patients treated with BioSeed-C with 2 years follow-up; symptom scores were significantly improved at both 1 and 2 years after baseline [59]. Reoperations occurred in 12.5% of patients including synovectomy (n = 2), debridement (n = 1), total knee arthroplasty (n = 1), and graft removal (n = 1) [59]. The mid-term outcomes of the same patient cohort with 4-years follow-up were reported by Kreuz et al. [62]. The authors note a durable symptom improvement over 4 years and a high rate of graft filling (mostly or completely filled in 43/44 patients on MRI assessment) [62]. In the subgroup analysis of 19 patients in this cohort with baseline osteoarthritis and a high grade focal defect, Kreuz et al. noted symptom improvement at 6–12 months which remained stable at 4 years as well as two clinical failures that went on to total knee arthroplasty (10.5%) [63].

3. Conclusions

In conclusion, short and mid-term clinical outcomes studies of MACT therapies for cartilage defects of the knee have been encouraging. However, commercial availability of MACT procedures is highly variable with respect to geographic region. Recent approval was granted in December 2016 by the FDA for use of MACI in the United States. To date this is the only MACT therapy available in this region. Availability is greater for multiple MACT therapies in Europe, though European Medicine Agency marketing approval for MACI was recently suspended in June 2016.

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