Second-Generation Autologous Chondrocyte Implantation: What to Expect

155

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Contents

Abstract

Chondral lesions are a challenging problem for the orthopaedic surgeon, and regenerative techniques have been widely studied in this field as ambitious solutions to restore the articular surface. Even though the clinical efficacy of autologous chondrocyte implantation (ACI) has been well demonstrated in the literature long-term follow-up, this technique presents some biological and surgical drawbacks. Second-generation ACI procedures have been developed to address these shortcomings. Different types of scaffolds have been applied clinically in numerous studies with promising results, but well-designed studies with long-term evaluation are still lacking. The versatility of the second-generation ACI approach has been shown by several studies that have successfully applied this procedure not only in the management of cartilage damage in young, active patients, but also in patients with OCD, patients over 40 years old, or in cases of degenerative lesions. However, besides overall good results, its superiority with respect to other surgical approaches is still controversial. Further studies are necessary to support the potential of second-generation ACI and to define better the correct indications for those patients who can have a real benefit from this regenerative treatment.

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Introduction

Chondral lesions are a challenging problem for the orthopaedic surgeon, and regenerative techniques have been widely studied in this field to recreate a hyaline-like tissue to restore as similar an articular surface as possible to the physiological one. The autologous chondrocyte implantation (ACI) technique was introduced in Sweden in 1987, and the first clinical trial on this topic was published in 1994 by Brittberg et al. showing satisfactory results in the treatment of isolated femoral condyle cartilage lesions (Brittberg et al. 1994). Although its clinical efficacy has been shown by several studies, the ACI technique has some biological drawbacks, including the risk of dedifferentiation of chondrocytes cultured on a monolayer structure and the inhomogeneous distribution of the liquid cell suspension in the lesion site; moreover, the surgical procedure is complex and not without morbidity (Kon et al. 2009a). Second-generation ACI procedures were developed to address these shortcomings: a three-dimensional biodegradable scaffold is employed as a cell carrier, facilitating implantation, which can be also performed arthroscopically (Marcacci et al. 2002; Erggelet et al. 2003); furthermore, the 3D structure has been shown to favor the maintenance of a chondrocyte-differentiated phenotype (Freed et al. 1993; Grigolo et al. 2002).

In recent years several scaffolds have been developed (Kon et al. 2009b), with substantial differences regarding the materials chosen, natural or synthetic, and their physical forms (Brittberg et al. 1994). Natural materials have the advantages of good biocompatibility, and they might also enhance cell proliferation; they include hyaluronic acid, collagen derivates, agarose, alginate, fibrin glue, and chitosan. Synthetic matrices, as not physiological components of the normal articular cartilage, may cause adverse effects on native tissue and implanted cells, even if chemical innovations developed in recent years have improved their biocharacteristics and biocompatibility; polylactic and polyglycolic acids are the most commonly used (Filardo et al. 2013a).

The surgical indications for this kind of treatment include posttraumatic or microtraumatic cartilage defects, but degenerative focal lesions and osteochondral defects have also been treated. However, indication criteria are still controversial (Filardo et al. 2012a, 2013a). Commonly recognized exclusion criteria are advanced whole joint pathology, such as extensive synovitis, knee instability, severe meniscus tears or malalignment, and immune-mediated pathologies or knee infection. Before surgery, it is necessary to evaluate by imaging the lesion size, the localization, and the involvement of subchondral bone (Gomoll et al. 2012) to confirm the treatment indications.

Regardless of the type of scaffold chosen, the surgical technique basically consists of two steps. The first one is a biopsy of healthy cartilage from a non-weight-bearing area for autologous chondrocyte culture. The second step is the arthroscopic or mini-open approach for the implant of the bioengineered tissue: after debridement, the scaffold is positioned on the lesion and fixation is obtained either by suture, resorbable pins, fibrin glue, or press-fit-only technique (Gomoll et al. 2012). With regard to the rehabilitation guidelines, the program is influenced mainly by lesion location: slower recovery has been reported in patellar lesions. Weight bearing is avoided for 3–4 weeks to allow the scaffold cohesion at the lesion site; in the meantime cycles of continuous passive motion (CPM) are allowed to recover an early full range of motion (ROM), promote defect healing, prevent the development of adhesions, and resolve the swelling. Full weight bearing is then permitted after 4–6 weeks, and patients usually return to normal activity 6 months after intervention and to high-impact sports after 1 year (De Girolamo et al. 2010). Complications following a second-generation ACI procedure can occur: a few cases of scaffold rejection and hardware failure due to a immune reaction have been reported; other drawbacks include scaffold migration and delamination in case of inadequate preparation of the implant site; less infrequent are swelling or fever in the first weeks and joint stiffness in the following months (Kon et al. 2009c).

Table 1 Bioengineered tissues employed in second-generation ACI: commercial name and composition

Product	Composition
MACI®	Porcine collagen type I/III matrix
HYALOGRAFT C®	Hyaluronic acid–benzilic ester matrix
BIOSEED C®	Fibrin + polyglycolic acid + polylactic acid + polydioxanone matrix
NOVOCART®	Collagen – chondroitin – sulfate matrix
CARTIPATCH®	Agarose – alginate hydrogel gel
ATELOCOLLAGEN®	Atelocollagen gel
CHONDRON®	Fibrin gel
NEOCART®	Collagen type I matrix
CARES®	Collagen type I hydrogel

Scaffolds in Second-Generation ACI

Scaffolds used in cartilage repair (Gomoll et al. 2012) can be based on components of the cartilage matrix (such as collagen or hyaluronan), proteins and natural polymers (such as fibrin, agarose, alginate, and chitosan), synthetic polyesters (such as polylactic acid, polyglycolic acid, polylactide glycolide, polyethylene oxide, and polypropylene oxide), or hydrogels (highly cross-linked hydrophilic polymer chains that yield a highly swollen, water-insoluble gel). The engineered materials used in the second-generation ACI techniques are illustrated in Table 1.

The most commonly used chondral matrices consist of collagen and hyaluronic acid. Since both are natural components of cartilage, they are able to integrate into the matrix and have been extensively used for ACI for more than a decade. The first scaffold employed in a second-generation ACI procedure was the Chondro-Gide® (Geistlich Biomaterials, Wolhusen, Switzerland) porcine collagen type I/III membrane; the MACI® technique (Genzyme, Naarden, Netherlands) consists of autologous chondrocytes seeded onto this bilayer porcine collagen I/III matrix, which is then implanted by arthrotomy. The first hyaluronan-based scaffold was Hyaff-11® (Fidia Advanced Biopolymers Laboratories, Abano Terme, Italy), a benzylic ester of the hyaluronic acid, where cells harvested from the patients are expanded and seeded in the Hyalograft C® procedure (Filardo et al. 2013a). BioSeed C® (BioTissue Technologies GmbH, Freiburg, Germany) is the most widely used synthetic scaffold. It is composed of fibrin, polylactic acid, polyglycolic acid, and polydioxanone. Its implant technique is characterized by a strong fixation obtained by reinforcing the corners with resorbable sutures. Several other options are now available on the market, but due to their recent introduction, they have been documented only by some preliminary studies (Filardo et al. 2013a).

What to Expect

The high number of publications that have dealt with cartilage repair treatment options suggests that cartilage surgery is no longer in its infancy. Some available treatments are now well-established options for cartilage repair, such as microfractures, autologous osteochondral transplantation, or fresh osteochondral allograft transplantation, and show satisfactory clinical outcomes in the long-term follow-up. However, with regard to cartilage regenerative options and especially second-generation ACI, whereas short- and midterm results are now available on small series of patients, the literature still lacks well-designed studies and patient evaluations with long-term follow-up. The analysis of results reported in some studies (Filardo et al. 2013a) highlights that not all patients can obtain the same benefit from these procedures and it would be necessary to define an individual profile, identifying patient- and lesion-specific aspects that

play a significant role in determining the prognosis, in order to apply the right treatment to the right patient. With regard to predictive factors for a good outcome after cartilage surgery, some of these are common among techniques, such as age and previous surgery, whereas others are more specific to the procedure considered. Age, degenerative etiology, and previous surgery are well-established critical factors since they are all variables that imply a more complex and challenging environment to address biologically and surgically. Other aspects are worthy of further discussion, such as female gender, lesion size, site of lesion, preoperative symptom duration, treatment of degenerative defects, or OCD. Concerning lesion size, there is in general a lack of correlation with the clinical outcome after second-generation ACI, but studies are mainly about medium-size defects, whereas less clear are the results for massive lesions. With regard to the lesion site, patellar lesions present the lowest improvement (Gobbi et al. 2009). The analysis of the influence of preoperative symptom duration shows that it is a critical factor, thus underlying the importance of appropriate timing for this treatment, especially in traumatic cases (Krishnan et al. 2006; Saris et al. 2009).

Concerning the treatment of degenerative lesions of articular cartilage with second-generation ACI, some additional problems have to be considered: degenerated alterations of joint environment include the disruption of the homeostasis and the release of inflammatory factors, such as cytokines and metalloproteasis. The implantation of a scaffold in this kind of joint environment may lead to an early failure of the graft attachment, which would not allow tissue regeneration. A recent publication (Filardo et al. 2012a) deals with the treatment of 54 patients affected by focal degenerative chondral lesions of the knee. The evaluation was performed up to 6 years with the IKDC, EQ-VAS, and Tegner scores. The results showed statistically significant improvements in all scores from the basal evaluation to the final follow-up; between the 2-year and 6-year follow-up, stable results were reported. Low physical activity level, female gender, and previous surgery were correlated with the poorest results; in fact, the percentage of improvement in the IKDC subjective score of patients that underwent previous surgery was lower than that of the other patients (respectively, 39 % $\pm$ 41 and 73 % $\pm$ 29). Despite the overall satisfactory results, an 18.5 % failure rate was reported.

The limits of a degenerated environment were further shown in another case series on patients with osteoarthritis, where second-generation ACI only offered a limited improvement. In fact, results in this challenging joint were significantly lower and failures increased to almost 30 % (Filardo et al. 2013b).

Age is also responsible for degenerative changes in the cartilage and joint environment, therefore impairing the healing potential; for this reason, most surgical treatments for cartilage regeneration are usually indicated in young people. However, if on one hand cartilaginous healing process capacity decreases with age and poorer results are expected when treating older patients with second-generation ACI, on the other hand there is a rising demand for high function from a population of no longer young but still active patients, who want to maintain their active lifestyle and hobbies. Furthermore, the treatment of cartilage lesions in older patients might also avoid or delay progressive joint degeneration and the need for more invasive procedures. A case series published by Kon et al. focused on the clinical outcome in the management of cartilage lesions with ACI techniques in patients with a minimum age of 40 years; the main purpose was to understand the real potential of these cell-based approaches in relation to aging. Sixty-one patients with International Cartilage Repair Society (ICRS) grade III to IV cartilaginous lesions of the condyles but no clear signs of osteoarthritis and over 40 years old were consecutively treated with second-generation ACI and evaluated for up to 5 years. Twenty-two patients were treated with Hyalograft C and 39 underwent the MACI procedure. A significant improvement in both subjective and objective evaluations was observed: the objective IKDC score increased from 20 % of normal and nearly normal knees before the treatment to 80 % at the final follow-up. A faster improvement was observed in the group treated

with the arthroscopic Hyalograft C technique, thus showing overall good results and the advantage of an arthroscopic approach. However, the high percentage of failures recorded in this patient category, which was 20 %, has to be underlined (Kon et al. 2011a).

In the field of chondral and osteochondral regeneration, the treatment of osteochondritis dissecans (OCD) of the knee is still an open question. OCD is an acquired lesion of the subchondral bone that may result in separation and instability of the overlying articular cartilage, characterized by a separation of an osteochondral fragment (Crawford and Safran 2006); several causes have been postulated but repetitive microtrauma correlated with potential vascular insufficiency is the most credited theory. Unstable lesions must be treated with a surgical approach because, if left untreated, they result in pain and osteoarthritis progression (Prakash and Learmonth 2002). Numerous surgical options are available to treat OCD (Pascual-Garrido et al. 2009); however, management of adult patients is controversial. In fact, the choice of the most suitable option depends largely on patient age, lesion size, and stability of the osteochondral fragment. Being an osteochondral pathology, the ACI approach needs to be modified with a step to restore the bone level. In a prospective study focusing on this modified second-generation ACI associated with bone grafting for the treatment of OCD, 34 knees were evaluated (Filardo et al. 2012b). A statistically significant improvement in all scores was observed after treatment: IKDC subjective score increased from the basal level of 38 ± 12 to 81 ± 20 at the final evaluation, and 91 % of the knees were rated as normal or nearly normal in the objective IKDC at the final evaluation. This study showed that second-generation ACI with autologous bone grafting can be a valid treatment option in the management of knee OCD. The implantation of an autologous bone graft offers the possibility to treat deep lesions as well, although poorer results in large lesions are a limitation of this surgical procedure.

Concerning gender, its influence on clinical outcome after surgical treatment with second-generation ACI has been recently reported (Kreuz et al. 2012). This prospective study investigated gender-dependent differences in the clinical and biomechanical results. Fifty-two patients (27 men, 25 women) were evaluated preoperatively and at 6, 12, and 48 months after surgery. A significant improvement in clinical scores was observed at the final follow-up both in women and men. Nevertheless, even though the defect size was larger in men compared to that of women, male patients achieved better clinical results at every follow-up than female patients in the KOOS score, and even isokinetic strength measurements in men were significantly higher compared to those of female patients. This gender-dependent different outcome may also be related to differences in neuromuscular coordination, muscle strength, and hormones: in fact, it seems that estrogens might negatively influence the chondral differentiation and matrix production, whereas muscle strength is an important factor in joint stability and production of cartilage during regeneration (Miller et al. 1993; Jenei-Lanzl et al. 2010).

Second-generation ACI may also be a good choice for the treatment of knee cartilage lesions in high-level athletes. Restoring the articular surface in knees under high-level stress is particularly challenging, but the hyaline-like tissue obtained with the regenerative cell-based approach offers highly demanding athletes a better functional recovery compared with the bone marrow stimulation approach (Kon et al. 2011b). In a comparative study, 41 high-level male soccer players with grade III to IV chondral lesions of the femoral condyle or trochlea were evaluated: 21 patients underwent second-generation ACI and 20 were treated with microfractures. All patients were evaluated preoperatively, at a 2-year and at a final 7.5-year mean follow-up. Both groups showed a statistically significant improvement in all clinical scores. The IKDC subjective score showed similar results at 2-year follow-up, but, at the final evaluation, better results were achieved with second-generation ACI. Both microfractures and second-generation ACI allowed athletes to return to pre-injury activity level at 2 years, although athletes treated by microfractures needed a median of 6.5 months to return to

training and a median of 8 months before the first official soccer game versus a median of 10.2 months for training and 12.5 before playing the first official game when treated by second-generation ACI. Whereas microfractures offer a faster recovery than second-generation ACI, this reparative treatment option is correlated with clinical deterioration in medium-term follow-up unlike regenerative treatment, which leads to the formation of a more hyaline-like tissue. Knutsen et al. (2004, 2007) reported that none of the failures after microfractures presented high-quality repair cartilage, thus suggesting that an inferior-quality repair tissue might increase the risk of failure or present a poorer outcome over time (Knutsen et al. 2004, 2007). That being so, in the management of cartilage lesions in high-level sport athletes, the regenerative approach might be preferable to microfractures, and it might be better to limit bone marrow stimulation in athletes in the final years of their career, who do not wish to stop playing for a long period or athletes risking contracts and career.

Finally, it should be underlined that the post-operative phase may also play a role in the clinical outcome: a recent study showed that intensive rehabilitation safely allows early return to competition without jeopardizing the clinical outcome and actually leads to better results at midterm follow-up (Della Villa et al. 2010).

Conclusion

Regenerative techniques can offer the replacement of the articular cartilage with a hyaline-like tissue, and the use of scaffolds has simplified and improved the potential of this treatment approach, but the properties of the healthy cartilage are still unmatched by any available substitute.

Clinical outcomes after second-generation ACI surgery showed good midterm results, with the advantages of implantation of autologous tissue and no risks of immunologic rejection. However, some disadvantages have to be reported. First of all this surgical approach is characterized by two steps and high costs. Furthermore, the donor site of autologous chondrocytes is not fully preserved from minimum morbidity; finally, extensive cell manipulation is required.

Until now, there is no agreement about the effective superiority of the regenerative approach over the others, and both results and indications remain controversial (Marcacci et al. 2013).

Clinical application is reported for different types of scaffold at short- and midterm follow-up with promising results, but well-designed studies with long-term evaluation are still lacking. The versatility of the second-generation ACI approach has been shown by studies that successfully applied this procedure not only for the management of cartilage damages in young active patients but also in patients suffering from OCD, patients over 40 years old, and in cases of degenerative lesions. However, further randomized controlled studies with long-term follow-up are necessary to confirm the potential of the second-generation ACI procedure and to better define the proper indications for this kind of treatment.

Cross-References

- ▶ Concussion in Sports Traumatology: Future Trends
- ▶ Nanotechnology in Sports Medicine
- ▶ Next-Generation Cartilage Solutions
- ▶ Osteochondral Talus Defects: Treatment by Biodegradable Scaffolds
- ▶ Rehabilitation after Knee Cartilage Transplantation with Autologous Chondrocytes or Stem Cells

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