Autologous chondrocyte implantation (ACI): an innovative technique for articular cartilage defects

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Abstract

Articular cartilage lesions can hardly be regenerated spontaneously in vivo, remain a challenging problem for orthopedic surgeons. Various techniques have been used to treat this pathology with variable success rates. In recent years, however, regenerative techniques, such as autologous chondrocyte implantation, have emerged as possible solutions for the treatment of chondral defects. The use of classic autologous chondrocyte implantation (first generation) has been associated with several limitations. To overcome these problems, a recent powerful cell based tissue engineering therapy has developed, Chondron™ as a commercial product of third generation autologous chondrocyte implantation. It consists of mixture of biodegradable and biocompatible gel with in vitro cultured autologous chondrocytes. This procedure avoids the use of periosteal flap, further simplifies the surgical procedure with limited time of operation with an arthroscopic procedure. Thus, the surgical morbidity and the recovery time for the patient are extremely reduced with no complications related to septic conditions and periosteal flap. The clinical outcomes of Chondron™ ACI have shown positively significant results.

Keywords ACI (Autologous chondrocyte implantation), Chondron™, chondral defects, tissue engineering

INTRODUCTION

Throughout a day, the knee joint undergoes a wide range of motion and stress. Sports injuries and heavy stress on knee joint may result in osteoarthritis, which represents structural breakdown of the synovial joint and is the leading cause of chronic disabilities. In addition, once injured, articular cartilage cannot be regenerated spontaneously in vivo.[1,2] Articular cartilage is largely devoid of nerve supply due to which early cartilage lesions might not be detected as pain. Often arthritis patients do not seek medical care until severe osteochondral lesions have formed.[3]

Osteoarthritis of knee is a common affection in India compared to the western world. In United States, arthritis is a major and foremost cause of disability in adults 2.2 times compared to heart disease.[4] There are an estimated 20 million Indians suffering from symptomatic knee arthritis.[5] Further, osteoarthritis strikes women more often than men and it increases in prevalence, incidence and severity after menopause[6,7] and it is estimated that more than 40% of all women over the age of 50 years are suffering from it.[8] Nearly 50% people at the age of 65 years have arthritis and it is recorded that more than 300,000 children are affected by arthritis.

CONVENTIONAL TECHNIQUES

Cartilage transfer is currently used only in the knee joint (and very rarely in the ankle) of individuals who have a small area of cartilage damage and not widespread arthritis. It is effective in cartilage defect where the size is small enough so that the plugs adequately fill the damaged area. In microfracture technique, the formation of fibro-cartilage occurs which has poor mechanical properties and does not resist cyclic loading and shearing force.[2] Further new cartilage that fills in the gaps is not the same as normal joint cartilage and will not hold up over time. The mosaicplasty results in the formation of patchwork or mosaic[9] and there is generally an occurrence of dead space between the grafts.[10] These flaws fail the conventional techniques in giving the promising results.

REGENERATIVE MEDICINES: ROLE OF ACI

Under these circumstances of tissue engineering, a powerful cell based therapy has proved a sustainable biological regeneration of damaged tissue or organs.

Autologous chondrocyte implantation (ACI), earlier also known as autologous cartilage transplantation (ACT) is an approach that has been used to treat defined, symptomatic knee cartilage defects. The important aspect of this treatment is to enable the regeneration of hyaline or hyaline like cartilage, and thus restoring the normal functions of a joint. Autologous chondrocyte implantation (ACI) involves the biological replacement of articular cartilage, first reported clinically by Brittberg et al.[1] and subsequently by several other authors[11–13] which has become an acceptable treatment option in appropriately indicated patients with symptomatic chondral defects.

There are three categories of ACI based on their modifications and advancement. The procedure for first generation ACI involves an arthroscopically performed biopsy of articular cartilage followed by implantation of cultured chondrocytes beneath

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a periosteal patch (Figure 1). The use of this classic autologous chondrocyte implantation (first generation) has been associated with several limitations related to the complexity and morbidity of the surgical procedure as well as frequent occurrence of the periosteal hypertrophy.[14–16] Further this technique requires arthrotomy, periosteal flap, prolonged operation time, big incision, postoperative complications and the process of rehabilitation is quite slow (Table 1).

Recent technological improvements in cartilage tissue engineering have aimed to overcome the intrinsic technical disadvantages of classic ACI by using artificial tissue constructs of autologous cells and biomaterials that function as a cell embedding component and/or as a scaffold for the formation of three dimensional tissues.[17] Second generation ACI used porcine collagen membrane as a substitute for the periosteal flap. There is no significant data for this technique as postoperatively some patients faced immunological problems and quality of tissue growth was unsatisfactory. The third generation ACI is also called as matrix induced autologous chondrocyte implantation (MACI) where the cells are seeded on membrane called matrix, such as hyaluronan[18] or collagen bilayer[19] and implanted on the damaged area (Figure 2). This doesn't require periosteal patch, further this is a sutureless fixation with reduced operative time as compared with first generation ACI. This technique is less invasive and fewer postoperative complications.

Third generation is an advancement of second generation where instead of matrix injectable gel is being used. This technique is becoming popular nowadays due to its efficient results and cost effectiveness as compared with first and second generation ACI.[20,21] This technique involves biodegradable and biocompatible gel mixed with in vitro cultured autologous chondrocytes and comparatively is a very easier operation than suture type. Further this technique enhances better cell maturation and better cell growth in vivo. The importance of the biodegradable scaffolds has been well documented by earlier workers which support the in vitro growth of highly viable chondrocytes and promote the expression of their original condrogenic phenotype.[22,23] Further this technique would be cost effective because it is more likely to produce hyaline cartilage, which is more likely to be durable and to prevent osteoarthritis in the long term.[24]

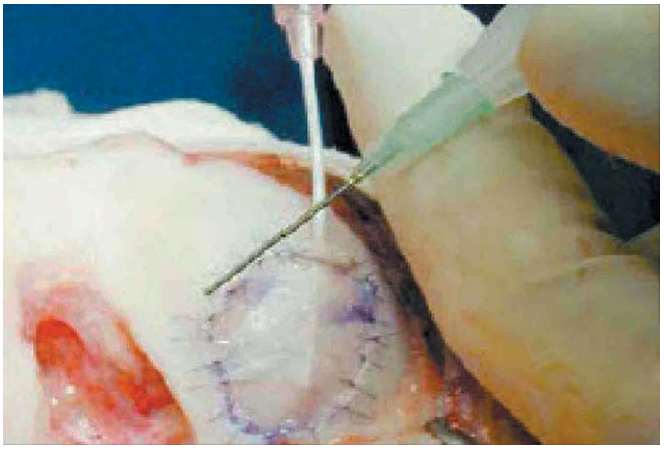


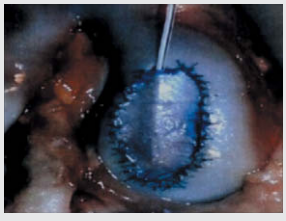
Figure 1 First generation autologous chondrocyte implantation (ACI; Source: Genzyme corporation, 2007).

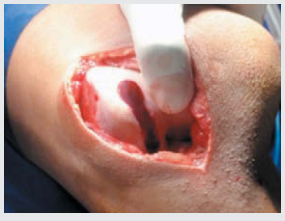
CHONDRON™*

Chondron™ is a third generation ACI product developed by RMS (Regenerative medicine services) a division of a Korean based company SewonCellontech. After 11 years of extensive research Chondron™ has received approval from Korea FDA (KFDA) in year 2001 as a first biotechnology product in Korea (Cartilage RMP: ACI using chondron).

Table 1 Comparison of first generation ACI (suture type) and third generation ACI (cell gel mixture).

	Suture type	Cell gel mixture
Operation time	Long (3–4 hours)	Short (20–30 min)
Incision	Big (>10 cm)	Small (<5 cm)
Surgical techniques	Slow	Fast
Application	Difficult (bursting, leakage)	Easy
Defective size	Small (less than 10 cm^2)	Large (up to 20 cm^2)





*Information about CHONDRON™ including rehabilitation care can be obtained from: Dr. Vinayak V. Kedage, Phone: 91-22-67330300-30. E-mail: vinayak@regrow.in

The general procedure for Chondron™ based ACI involves the identification and confirmation of defected area through arthroscopy and then if the defect is decided to be recovered with Chondron™ implantation, a small biopsy is implemented from patient's healthy femoral articular cartilage in the less weight bearing area. Once normal cartilage is harvested it is sent for cell culture to a specialized GMP facility for a period of 4 weeks (Figure 3) where the cells are increased up to 48 millions. Each single injectable vial of Chondron™ contains approximately 12 million cultured autologous chondrocytes in 0.4 ml of culture solution (Figure 4). The cell viability is evaluated to be over 80%. Fibrin gel is mixed with cultured chondrocytes and injected in to patient's cartilage defect area (Figure 5).

Chondron™ has many advantages over other techniques such as fast and effective repair, highly evaluated in safety and efficacy and permanent repair of cartilage. This is a viable technique for the prevention of osteoarthritis rather than its cure against the existing conventional techniques.

The clinical outcome in patients of Chondron™ ACI for the repair of chondral defects of the knee has shown significant results.[20] This product has been commercialized since the last 7 years and the clinical study protocol has been approved by KFDA. The clinical results are based on the case reports from 261 patients (166 male, 92 female and 3 unknown) with average defect size of 4.91 cm^2 (range 0.7–20 cm^2). From the study, 93.87% of all patients showed statistically significant improvement at 6 months postoperative follow-up which is higher as compared to the other study.[21] This clinical data strongly supports the efficacy and safety of Chondron™ use.

Permanent repair of cartilage gives new hope for patients to live in the healthy & active life because ACI is the fundamental treatment for cartilage defects. The fourth generation ACI by using

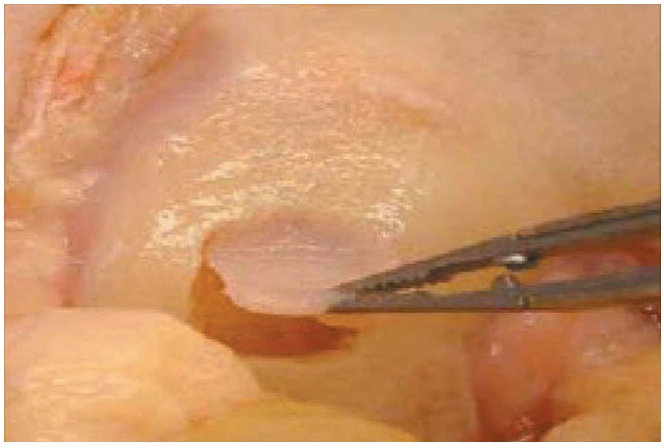


Figure 2 Second generation autologous chondrocyte implantation (ACI; Source: Genzyme corporation, 2007).

Figure 4 In vitro cultured chondrocytes (© RMS–Regrow®, 2008).

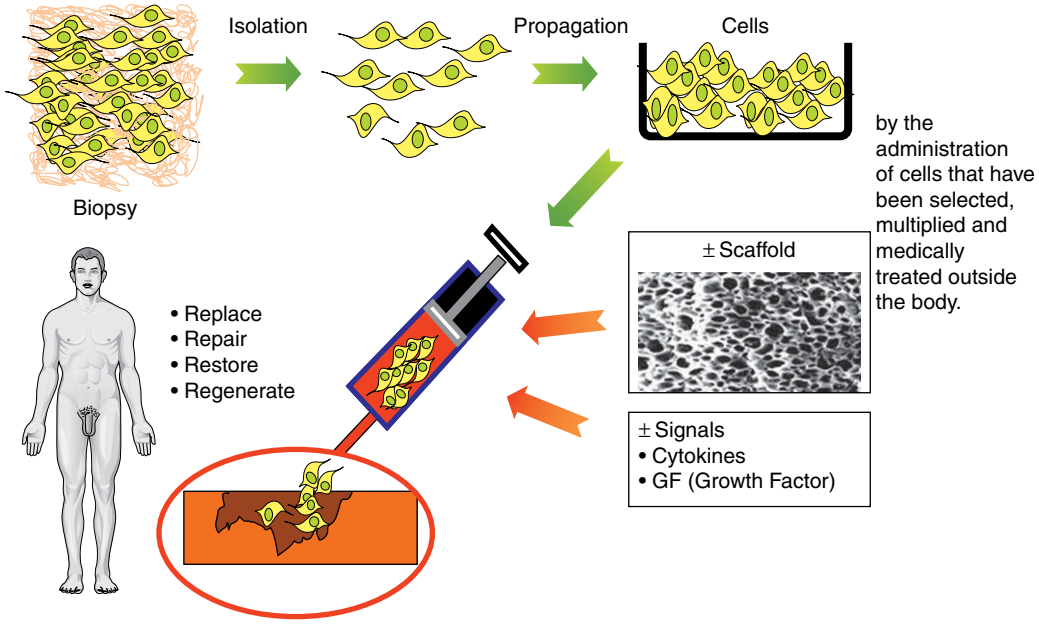


Figure 3 Outline for the third generation autologous chondrocyte implantation (ACI; © RMS–Regrow®, 2008).

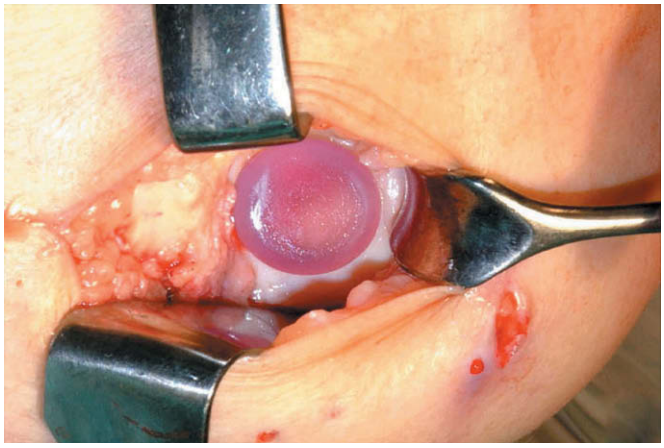


Figure 5 Third generation autologous chondrocyte implantation (ACI; © RMS–Regrow®, 2008).

Chondron™ will be an ultimate optimal solution against various problems raised by autografts or allografts such as donor site morbidities, immunologic problem and implant loosening.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. ♦

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