

Current and Future Trend in Articular Cartilage Restoration

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Introduction

Cartilage restoration has evolved from the very limited use of fresh osteochondral allografts by a few centers (e.g., Gross, Convery, and Meyers) to the widespread use of marrow stimulation today and the lower volume techniques of osteochondral autograft and cultured chondrocyte implantation. While the scientific goal of articular cartilage restoration is to recreate normal hyaline cartilage at the site of a cartilage defect, at present this has only been achieved through osteochondral transfer, noting that limitations of autograft and allograft implants preclude widespread use. While hyaline-like tissue properties may be demonstrated using cell therapy alone, the tissue lacks the natural stratification of normal hyaline cartilage. However, the clinical goal in each of these cartilage surgeries is pain free normal function with a durable implant. With increased emphasis on costs, it may not be necessary for all techniques to yield hyaline like cartilage, but rather to satisfy patient goals. That is, while laudable, stratified hyaline cartilage may not be necessary to meet these goals. In fact, currently when evaluating new clinical cartilage restoration techniques, the FDA does not request biopsies for histomorphology, but rather they require patient reported outcomes as the primary endpoint. This is typically pain or, when there are co-primary endpoints, the endpoints are pain and functional activity level. Therefore, as one explores future trends in the technique of cartilage restoration, the demand match approach is useful; applying the optimal technique to benefit the specific cartilage lesion of a specific patient in a cost efficient manner.

Osteochondral Allograft

Bugbee et al¹ recently reported the largest series of osteochondral allograft (OCA) with follow up as long as 19.5 years. The PROs (patient reported outcomes) results for monopolar OCA continue to be approximately 76% good/excellent, while bipolar typically in the range of 50% positive. The number of transplants per year has been relatively stable in the range of 1-2,000/year as surgical challenges limit the number of interested surgeons and availability continues to be a limiting factor. Currently, extensive testing necessitates a delay of 10-14 days from harvest to availability for transplant. As the chondrocyte viability decreases with storage time, most tissue banks expire the tissue at 28 days. To extend the shelf life, various alternative medias have been tried and most recently, Bugbee et al² showed improved chondrocyte viability of OCA stored at 37° Centigrade instead of the classic 4° Centigrade. At the time of transplant, the chondrocytes are vulnerable to impaction forces and may be easily die with standard levels of impaction. The trend is to use thin (6-8 mm) composites that are beveled and use only finger pressure to press-fit the plug in the socket. This thinner construct also speeds the time of incorporation through creeping substitution by requiring less allograft bone.

Williams et al³ showed viability is also affected negatively during the post operative environment (hemarthrosis) and this may be an area for optimization. To expand availability, a variety of freezing techniques have been tried, but even those with cryo-preservation have not yielded consistent outcomes. That led to a search for other ways to preserve the tissue. One approach is to stabilize the matrix and allow all the cells to die. In one example of this technique, the matrix is stabilized by cross linking with methylene blue. Animal studies are promising and human trials are to begin shortly.

It is typically stated that OCA are immune-privileged, yet a percentage of patients become antibody positive after OCA transplantation⁴. When Bugbee et al⁴ compared PROs, those that were antibody positive had less favorable outcomes than those that are antibody negative. This antibody response is primarily to the bony portion of the graft—probably the soft tissue remnants within the subchondral bone. Thus, the thin OCA constructs noted above that allow pulsatile irrigation to more thoroughly clean the bone, may decrease the extent of an immunogenic response. Carried to the extreme, removal of all bone would negate immunogenic response, yet pure cartilage shells do not integrate with host bone. However, if the cartilage is particulated, the chondrocytes escape, multiply and form new matrix. While this has been shown to occur in the animal model, the Cartilage Restoration Center of Indiana has submitted for publication the first prospective case series using this technique: DeNovo NT (IsTo St. Louis MO and Zimmer, Warsaw IN)

Marrow Stimulation

Marrow stimulation is the generic term for the techniques that allow marrow cells to enter from the subchondral bone. The goal for the “marrow derived cells” is to create hyaline-like cartilage when exposed to the appropriate post operative mechanical environment (continuous passive motion and protected weight bearing). This term may be a misnomer as there is typically little or no red marrow in subchondral knee bone. Rather, most of the pluripotential cells in the clot are probably similar in origin to any other clot that occurs throughout the body—blood derived and local tissue derived. Regardless, numerous studies show a wide range of fibrocartilage to hyaline-like cartilage with this technique. The preservation of the mechanical and biologic integrity of the subchondral bone plate is important for clinical success. As it is technically difficult to reproducibly “lightly burr” the subchondral plate without weakening it, drilling and microfracture, as popularized by Steadman⁵, are more commonly used than abrasion arthroplasty technique. One of the reported advantages of marrow stimulation over drilling was that microfracture would not cause the thermal necrosis thought possible with drilling. However, this concern is being challenged by Buschmann et al⁶ as they demonstrated in an animal model that drilling does not cause thermal injury

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and that the drill holes allow more consistent channels for cell migration compared to microfracture. Regardless of whether the technique is drilling or microfracture, the ease of performing an all-arthroscopic inexpensive “marrow stimulation” procedure and the acceptable results in small to medium sized cartilage lesions has resulted in this being the most widely used cartilage restoration procedure in the United States.

Expanding on marrow stimulation, the goals are to improve the hyaline-like characteristics and durability of the resultant tissue. One option is to increase the number of available adult stem cells using true hemopoietic marrow harvested from the iliac crest. The marrow or concentrated stem cells are then transferred to a microfracture-prepared bed. Another approach is to apply an acellular scaffold for cells to organize (autologous membrane induced chondrogenesis or AMIC). There are many scaffold variants ranging from a true physical membrane to a biphasic liquid hydrogel that congeals *in situ*. Finally, it may be possible to further influence the pluripotential cells with growth factors, such as reported with OP-1.⁷

Osteochondral Autografts

Morgan (United States) and Bobic (United Kingdom)⁸ developed the technique of harvesting moderate sized osteochondral (OC) plugs (8-12 mm) and transferring them to focal cartilage defects. During the same time period, Hangody (Hungary)⁹ used smaller OC plugs (4-8mm) to create a mosaicplasty at the recipient site. Currently, efforts are directed at diminishing harvest site morbidity (pain and hemarthrosis) by back filling the harvest sites and using laboratory data to select the harvest site. Cole¹⁰ demonstrated there is less stress at the intersection of the trochlea and the medial femoral condyle than the site of classic harvest laterally. When harvest sites are unknown, there are subsets of patients who experience pain at these sites.

Science will continue to guide optimization of the technique. For example, to avoid chondrocyte death minimal force is applied to the cartilage to seat the plug. The plug needs to be flush with the surrounding cartilage to avoid increased stress on the opposing articular surface. Expanding on this concept, synthetic plugs may have the capacity to reform bone and cartilage in the defects (see cell free scaffolds below).

Cultured Chondrocyte Implantation

The rapidly exploding field of cell therapy to treat articular cartilage defects is based on the pioneering work of Dr. Lars Peterson. The basics of the technique are still used today and for the foreseeable future. As a two-stage technique, the first stage is a biopsy of healthy articular cartilage harvested arthroscopically from a low load area of the knee. The matrix is enzymatically degraded to release the chondrocytes. The chondrocytes expand in a monolayer culture (where they dedifferentiate into spindle cells) creating more than 10 million cells from only the few hundred thousand cells in the original biopsy. The cell suspension is then injected

beneath a periosteal patch or collagen substitute¹¹, where they differentiate to chondrocytes and produce matrix. Two companies now assay the cells to assure this potential (Genzyme VIP and Tigenix ChondroSelect). Since the work of Peterson, there have been many modifications for the use of autologous chondrocyte implantation (ACI).

The timing and action of the cells in culture may be modified with various factors. For example, fibroblast growth factor (FGF) is used by Prochon which requires fewer cells at harvest and less time to implantation while maintaining a higher chondrocytic phenotype. This is just the start of cell manipulation during culturing with the end goal of creating cells that reproducibly form hyaline cartilage. Using this same technique, it is possible to use allograft cells. With one product, DeNovo NT, infantile chondrocytes have a robust cell and matrix response. The chondrocytes are so robust that disks of neocartilage are formed without the need for a scaffold. The safety and feasibility has been shown clinically in a three center (the Cartilage Restoration Center of Indiana [CRCI] being one such center) Phase I-II study of DeNovo ET (IsTo, St. Louis MO and Zimmer, Warsaw, IN).

The original technique used autologous periosteum to form a water tighter cover over the chondrocyte suspension. This often resulted in periosteal overgrowth, which required subsequent surgery (usually chondroplasty). To obviate this problem, a variety of scaffolds have been used in place of the periosteum with clinical outcomes similar to ACI. Initially, these largely collagen membranes (C-ACI) were used in the same manner as the periosteum and thus the term Collagen-ACI or C-ACI originated. This technique was then modified by Steinwach¹² who seeded the cell suspension on the scaffold. After cell adherence the patch is implanted. Finally, many companies are providing a construct that result from seeding the cells onto a scaffold during the culturing process. This allows a physically robust chondrocyte/scaffold construct that allows arthroscopic implantation.

Converting this two-stage procedure to a one-stage procedure is appealing to patients and insurance companies alike. As with the DeNovo NT mentioned above, it is possible to mine autologous cartilage at the time of surgery, implant it and have it grow “new cartilage” as reported at ICRS Poland in 2007 by CRCI¹³. A prospective properly powered randomized control phase 3 trial is now under way to evaluate clinical efficacy of this technique (Cartilage Autologous Implant System CAIS). Future modifications of each of these techniques will focus on arthroscopic applications, efficacy and cost effectiveness.

Scaffold Use in Cartilage Restoration

Scaffolds are currently not approved for cartilage restoration in the United States for clinical use outside of FDA approved trials. Outside the US, scaffold use in cartilage surgery is more prevalent than the original cell suspension ACI technique. Scaffolds are often categorized by their structure (monophasic, biphasic, multiphasic, etc.) and/or if they are used “with” or “without” cells. To be clear as to the

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mechanism of action, the term should be “scaffolds without cells at implantation,” as these scaffolds function by providing structural guidance for endogenous pluripotential cells, which rapidly populate them. Tables 1-3 list the preclinical and non-

US clinically available scaffolds. For detailed information of the basic science and clinical applications please refer to the chapter by Gomoll and Farr.¹⁴

Table 1
Scaffolds Without Cells At Time of Implantation (Host Cell Source)

Scaffold Type	Product Name	Manufacturer
Autologous Matrix Induced Chondrogenesis	AMIC®	Geistlich Biomaterials ¹⁵
Matrix modulated marrow stimulation	BST CarGel™	BioSyntech ¹⁶
	GelrinC™	Regentis Biomaterials ¹⁷
	PGA, Hyaluronan, Autologous Serum	(combination)
	ChonDux™	Cartilix ¹⁸ (subsidiary of Biomet)
Multiphase scaffold to fill osteochondral defect	TRUFIT∠ CB Plug™	Smith & Nephew ¹⁹
	Maioregen®	Finceramica ²⁰
	Chondromimetic™	Orthomimetics ²¹
	CR-Plug®	RTI Biologics ²²
	ASEED® Scaffold	Interface Biotech ²³

Table 2
Scaffolds With Seeded Cells (Single-Stage)

Product Type	Product Name	Manufacturer
Collagen patch seeded	ACT-Cs: ACT (Autologous Chondrocyte Transplant)	(combination)
Cartilage Autograft Implant System	CAIS™	DePuy/Mitek, Inc. ²⁴
Cell replacement technology	Cell Replacement Technology™ (CRT) Instruct™ Products	CellCoTec™ ²⁵

Table 3
Scaffolds With Cells Cultured On/Within Scaffold (Two-Stage)

Product Name	Manufacturer
MACI™ (Matrix Associated ACI)	Genzyme ²⁶
CartiGro® ACT on Chondro-Gide	Stryker ²⁷ /Geistlich Surgery ¹⁵
NeoCart™	Histogenics ²⁸
CaRes®	ArthroKinetics ²⁹
Hyalograft C™ (<i>Hyaff-11 HA Polymer</i>)	Fidia Farmaceutici S.p.A. ³⁰
Bioseed C®	BioTissue Technologies GmbH ³¹
Cartipatch®	TBF Banque de tissus ³²
Novocart 3D®	TETEC® Tissue Engineering Technologies AG ³³
The BioCart™	ProChon Biotech, LTD ³⁴
Cartilink®-3 for Autologous Chondrocyte Implantation (ACI)	Interface Biotech ²³

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