Current Status of Autologous Chondrocyte Implantation

By Brian Cole, MD, and Shane Nho, MS

In the late 1980s, Lars Peterson, MD, initiated the use of cultured chondrocytes implanted beneath a periosteal patch as a treatment for chondral injuries. Animal studies demonstrating hyaline-like repair and encouraging early clinical results led to the widespread implementation of autologous chondrocyte implantation (ACI) in the United States and Europe with clinical and basic science studies supporting the long-term efficacy and durability of ACI. However, there are a number of scientists investigating alternative methods of enhancing the biological repair and the surgical technique using ACI.

ACI Clinical Outcomes

Mid-term ACI results have reported approximately 85% improvement of femoral lesions and osteochondritis dissecans (OCD).[1,2] Chondral defects of the patella and tibia have been known to be difficult areas to repair; thus, the results have been much less predictable. Minas compared the clinical outcomes of patients in 3 different groups: simple (mean size, 4.30 cm^2), complex (6.75 cm^2), and salvage (11.66 cm^2) groups at 24 months.[3] The patients of complex and salvage groups usually required additional procedures to correct alignment or ligament insufficiency. Patients in the simple and complex group demonstrated high functional improvements, but the patients in the salvage group had the highest satisfaction rating of 90% compared to 50% in the simple group and 80% in the complex group.

Vasara and associates[4] performed second-look arthroscopy with electromechanical indenter testing 1 year following ACI of the knee. Fifteen of 29 patients rated their knee as good or excellent by the Brittberg score, but 20 patients had follow-up scores greater than baseline scores. Arthroscopy demonstrated lesions filled with repair tissue with generally good integration with the surrounding cartilage, and periosteal hypertrophy was evident on several occasions. The average indenter stiffness of the implantation site was roughly 65% of the surrounding normal cartilage. The OCD lesions tended to be lower at 42% than the traumatic lesions at 72%. Vasara et al concluded that the indentation analysis did not correlate with clinical evaluation at 1 year because the tissue healing and remodeling process is not yet complete.

Innovations in ACI

Despite the success of ACI, there is considerable interest in improving and expanding this new technology. A suitable substitute for the periosteal patch is one modification that has received significant attention. Regarding the current periosteal patch, there are concerns of periosteal hypertrophy, delamination, dedifferentiation of chondrocytes, donor site morbidity, and uneven distribution of chondrocytes beneath the patch.

Collagen membrane and hyaluronan scaffolds appear to be the most promising and have already been implanted in human subjects.

Different variations of the collagen matrix scaffold are being investigated by a number of groups. Mahroof et al[5] have implanted the chondral lesions (mean, 2.88 cm^2) of 34 patients with a porcine collagen type I/III membrane and autologous cells. With an average follow-up of 19 months, 68% of patients have good or excellent Brittberg ratings and improvements in Lysholm scores. Arthroscopy demonstrated good implant integration with surrounding normal cartilage, and 70% of biopsies confirmed the presence of hyaline cartilage. Bentley et al[6] implanted the chondral defects (mean, 4.35 cm^2) of 125 patients with autologous cells using either traditional periosteum (26%) or porcine collagen membrane (74%). At 1 year patients reported 89% good or excellent ICRS ratings and second-look arthroscopy of 61 patients revealed 82% ICRS grade 1 or 2 repair. Granrath et al[7] reported that patients implanted with collagen fleece scaffold coated with autologous cells demonstrate good clinical results and well-restored joint surface by MRI. Second-look arthroscopy reveals no scaffold hypertrophy or ossification of the graft, and biopsies confirmed collagen-like repair similar to adjacent cartilage with regard to microscopic, biomechanical, and viscoelastic patterns. Other collagen-based scaffolds that are under consideration include collagen tri-layer matrix, three-dimensional collagen sponge, and chitosan blended collagen scaffold.

Hyaluronic acid based polymer (Hyaff-11, Fidia Advanced Biopolymers, Italy) is a biodegradable, 3-dimensional biologic scaffold. Facchini et al[8] conducted studies to determine the ability of this biomaterial to support the growth of human chondrocytes. Proteoglycan and collagen type II production were noted with time and chondrocytes completely colonized the scaffold. Nehrer et al[9] reported the preliminary results of the human experience with the hyaluronan matrix (Hyalograft C, Fidia Advanced Biopolymers, Italy). Twenty-three patients with a mean defect size of 6.2 cm^2 in the femoral condyles and patella were implanted. After 6 months, the average VAS-Scale decreased to 16.4 (nearly no pain) from a preoperative score of 77.9 (severe pain). This technique requires a smaller incision with fibrin glue fixation. It is thought that the 3-dimensional matrix should be able to provide a more uniform distribution of chondrocytes in the chondral defect. Preliminary studies are also being conducted on agarose gel, calcium phosphate cement, polylactide and polyglycolide sponge, 3D polysaccharide scaffold, polyethylene glycol terephthalate-polybutylene terephthalate block copolymer scaffold, polyurethane scaffold, perforated polyurethane prosthesis, biphase hydrogel beads, and cartilage-like biomaterial.

In addition to the biologic scaffold, there are a number of institutions that are conducting research involving chondrocyte culture techniques, cryopreservation of chondrocytes, periosteum evaluation, growth factor augmentation, and the use of stem cells. The next generation of ACI should use a biologic scaffold that is able to transport and sustain chondroctyes without adverse reactions. A 3-dimensional matrix may provide more uniform chondrocyte distribution in the defect and relative ease of surgical implantation that may permit the orthopaedic surgeon to perform the procedure with an arthroscopic or arthroscopically-assisted approach. Purification of chondrocyte culture techniques and augmentation with growth factors may prevent dedifferentiation of chondrocytes, thereby facilitating the production of hyaline cartilage. The early term clinical results of collagen and hyaluronan scaffolds are promising and seem to at least parallel traditional ACI outcomes.

Further scientific and clinical studies are necessary to determine which modifications to ACI may yield the best possible results. A focus on decreased processing costs, biologic carriers, and less invasive techniques is likely to dominate these future efforts. ■

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References

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