Regenerative Musculoskeletal Care: Ensuring Practice Implementation

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The first human cartilage cell transplantation, in 1987, opened the field of regenerative musculoskeletal care. The regenerative (r)evolution has transitioned into a "technovolution" in which ingenuity and creativity enable solutions that improve quality of life. Ongoing development of regenerative strategies showcases a recognized priority in musculoskeletal care. Initial regenerative therapies are successful; treatment options remain confined to trials in specialized clinics. Thus, new cellular regenerative therapies are being introduced, but adoption in daily practice remains elusive.

Regenerative therapies are integral in advancing musculoskeletal care options. Science-driven clinical trial experience has informed best practices while recognizing limitations in product development plans and regulatory frameworks impeding seamless adoption. Transnational collaborative efforts are needed to ensure standardization and expedited implementation of clinically ready therapies.

REGENERATION: AN ENDURING QUEST

Restorative surgical medicine dates as early as 6,500 BC Egyptian recipes for treatment of burns and skull trepanation described by Hippocrates or Aztec for branch intramedullary fixation of fractures all illustrate the profound human aspiration to "repair defects in nature." Today, this quest is particularly vibrant fueled by advances in regenerative sciences.

Articular cartilage damage typifies a prevalent disease spectrum culminating in end-stage osteoarthritis. Cartilage degeneration affects a million people in the United States alone, presenting a major challenge due to the limited innate ability for cartilage healing. In fact, knee arthroscopy reveals that over 60% of orthopedic patients have a chondral or osteochondral defect. Although initial regenerative therapies have proven successful, treatment options remain confined to controlled trials offered within specialized clinics. Thus, while new cellular and noncellular regenerative therapies are being introduced, adoption in daily practice remains elusive.

REGENERATIVE THERAPIES FOR ARTICULAR CARTILAGE REPAIR

From the first cell therapy applied to the human knee, a surge in implantation techniques resulted in the roll-out of autologous chondrocyte implantation (ACI) regimens.[1] In first generation ACI, a biopsy from a nonweight bearing area procures chondrocytes, which are expanded before re-implantation under an autologous periosteal cover. In second generation ACI, a collagen or bioresorbable membrane has replaced the periosteal cover to prevent periosteal complications and improve surgical efficiency and reproducibility. The third generation, in which cells are implanted in an open-structured 3D collagen matrix, was recently US Food and Drug Administration (FDA) approved in combination with release criteria for potency of the cellular product. The majority of ACI's are performed using mini-arthrotomy. Although arthroscopic approaches are used by some, cellular viability may be decreased by the excessive handling involved. Two decades of randomized trial experience demonstrating favorable outcome has stimulated introduction of cell-based regenerative solutions as standard of care in specialized clinics.[1] The burden on patients who have to undergo typically two surgeries, high costs, limited access, and insurance coverage, along with stringent policies, became a limitation to broad implementation stimulating development of fourth generation solutions.

Focus is placed on single-stage procedures with lower costs. Both autologous and allogeneic medicinal signaling cells (e.g., mesenchymal stem cells (MSCs)) derived from different tissues, such as bone marrow, fat, and synovium are explored. The added value of combining MSCs with cartilage is their enhanced capability to stimulate cartilaginous regeneration, streamlining the procedure. Autologous MSCs and bone-marrow concentrates are increasingly being used for cartilage repair. In parallel, implantation of bone-marrow derived MSCs with ACI is considered. The evolving premise is that MSCs are as effective as chondrocytes. Repair of chondral injuries using a hyaluronic acid-based scaffold with activated bone marrow aspirate concentrate has shown promise with durable cartilage repair after 5

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Table 1 Overview of studies applying MSCs for cartilage defect repair in the knee

Cell type	Study type	No. of patients	Follow-up	Results	Clinical-trials.gov identifier
BMMSC	Case report	2	60 months	Clinical improvement and defect fill with fibrocartilage	
BMMSC	Case report	1	12 months	Bone and cartilage repair	
BMMSC	Case report	3	17–27 months	Clinical improvement and defect fill with fibrocartilage	
BMMSC	Case report	1	12 months	Clinical improvement and defect fill with hyaline tissue	
BMMSC	Case series	5	12 months	Clinical improvement and defect fill	
BMMSC	Case report	2	31 months	Clinical improvement and defect fill	
BMC	Case series	48	48 months	Clinical improvement and defect fill	
BMC	Case series	20	24 months	Bone and cartilage repair	
BMC	Case series	5	12 months	Defect fill with hyaline to fibrocartilaginous tissue	
BMC	Case series	54	60 months	Clinical improvement and good integration of repair tissue	
BMC	Case series	15	24 months	Clinical improvement and defect fill with hyaline tissue	
BMC and AC	Phase I/II study	40	24 months	Clinical improvement and defect fill with hyaline tissue	NCT01041885
SMSC	Case series				
BMMSC	Comparative case series	36 (total 72)	24 months	Clinical improvement, defect fill with hyaline tissue	
BMC	Comparative case series	25 (total 81)	36 months	Clinical improvement and defect fill with hyaline tissue	
PBMSC or BMC	Comparative case series	25 PBMSC, 21 BMC	60 months	Clinical improvement and defect fill for both groups	
BMMSC	Case series	25	12 months		NCT00891501
BMMSC	Case series	6	12 months		NCT00850187
BMC	Case series	140	36 months		NCT02005861
BMC	Case series	50	12 months		NCT01159899
ATSVF	Comparative study	40	24 months		NCT02090140
ATMSC	Comparative study	30	18 months		NCT01399749
BMMSC	Comparative study	50	60 months		NCT00885729
Allogeneic UMSC	Phase III study	104	48 weeks	Safe application and repair with hyaline tissue	NCT01041001
Allogeneic UMSC	Phase III study	103	60 months		NCT01626677
Allogeneic UMSC	Phase I/II study	12	24 months		NCT01733186
Allogeneic SMSC	Case series				
Allogeneic BMMSC with AC	Phase I/II study	35	18 months	Safe application and repair with hyaline tissue	NCT02037204

AC, autologous chondrocytes or chondrons; ATMSC, adipose tissue derived mesenchymal stromal cell; ATSVF, adipose tissue stromal vascular fraction; BMC, bone marrow concentrate; BMMSC, bone marrow derived mesenchymal stromal cell; MSC, mesenchymal stromal cell; PBMSC, peripheral blood derived mesenchymal stromal cell; SMSC, synovium-derived mesenchymal stromal cell; UMSC, umbilical cord blood derived mesenchymal stromal cell.

years compared with alternative options, including microfracture (subchondral penetration stimulating intrinsic fibrous tissue repair).[2] Further therapeutic optimization, including use of lineage-specification and preconditioned strategies, is yet to be implemented. Recently finished and ongoing clinical trials testing MSCs cell therapy for cartilage defect repair are summarized in **Table 1**.

REGULATORY LANDSCAPE

In 2011, the first Advanced Therapeutic Medicinal Product (ATMP) for cartilage repair was registered by the European Medicine Agency. Reimbursement was secured in a limited number of countries and cellular alternatives remained on the market without ATMP registration, eventually prompting the main ACI provider to withdraw the product (ChrondroCelect) from the European market. This experience opens the debate on how accumulated (pre)clinical results and an exemplary safety profile can be reconciled with more recently developed regulatory guidelines. Several countries, such as Germany, Switzerland, and Italy, use an augmented microfracture technique (autologous matrix-induced chondrogenesis), in which penetrations in the subchondral bone are covered with a collagen membrane to allow fibrous tissue repair. In Italy, repair of chondral injuries using a hyaluronic acid-based scaffold with activated bone marrow aspirate concentrate is increasingly popular. In the Netherlands, allogeneic MSCs mixed with recycled, defect-derived autologous chondrons are used for the treatment of cartilage defects in early trials. Safety and initial clinical outcomes were documented using this IMPACT technology.[3] DNA short tandem repeat analysis indicates that newly formed tissue contains patient-only DNA, suggesting that allogeneic MSCs stimulate a regenerative host response. Although cellular therapies are promising, to realize such treatments in clinical practice improved coordination across medical and regulatory communities is needed. Whereas Europe aims at a homogenous regulation and registration of ATMPs in the European Clinical Trials Database (EudraCT), there is variation in marketing, clinical practice guidelines, local and central regulation, as well as reimbursement policies.

In the United States, few FDA approved options exist for knee cartilage defects. The first FDA approved cell therapy for cartilage repair was Carticel ACI. This two-stage *ex vivo* cell-expansion technique obtained approval under an accelerated path with clinical data from Europe, preregulation data from the United States, and a commitment for postmarket surveillance. Since that time, however, cartilage repair technologies face a much more arduous task of approval to market. Cartilage cell therapies can receive approval as a drug, device, or biologic under current FDA regulatory pathways.[4]

Due to the precedent of Carticel, most cell therapies are evaluated under a biologics pathway. Due to these significant challenges, there have been no further FDA approved therapies. However, there are some promising technologies on the horizon. For example, Neocart (Histogenics) recently completed enrollment of almost 250 patients in a multicenter phase III trial in the United States.

In 2017, third generation ACI, or MACI, was FDA approved for cartilage defects of the knee in the United States. MACI (autologous cultured chondrocytes on porcine collagen) has now replaced Carticel. Interestingly, MACI received FDA approval largely based on data from clinical trials in Europe, not centered on any trials in the United States. Due to the cost of typical regulatory approval, many new products for treatment of cartilage defects in the United States over the past 10 years have been allograft tissue. Allograft tissue, including cells, tissues, and tissue-based products that are: (1) used in a homologous fashion; (2) that are minimally manipulated; (3) have no systemic effects; and (4) are not used in combination with other products, are considered donor tissue and do not require a marketing application with clinical safety and efficacy data. Human cells, tissues, and cellular and tissue-based products (HCT/Ps) not meeting all four criteria are regulated as drugs, biologic drugs, or medical devices.

For MSCs, the regulatory process can be different. For most musculoskeletal/cartilage repair indications, the adult MSC is most commonly utilized. If this cell is minimally manipulated and used in a homologous fashion, then it falls under physician-directed use. For example, mononuclear cells can be isolated from bone marrow or adipose tissue with only aspiration and centrifugation steps, so without tissue digestion. A small portion of these mononuclear cells is MSC. This isolation process would be considered minimally manipulated. In contrast, MSCs that require culture expansion to create larger numbers are in the same regulatory category as mass-produced drugs. This drug category includes using any cultured cell for a nonhomologous use, such as expanded MSCs for cartilage repair. Therefore, the pace of development may be more defined by regulatory pathways that the actual biologic effect of the MSCs themselves.

PRACTICE PERSPECTIVE

To date, thousands of patients have been treated by ACI. A recent long-term follow-up study of treatment of articular cartilage defects with cell therapy suggested that ACI did not outperform the noncellular microfracture technique.[5] As microfracture is a single-stage surgery, these findings would suggest microfracture would be more cost-effective. However, this is the only trial that did not show superiority of cell therapy over conventional treatments. Using ACI to treat larger and more complex cartilage defects seems to be clinically advisable and more cost-effective in the long-term.

Although MSCs and MSC-rich concentrates are promising for cartilage repair, a lack of comparative studies precludes determination of what the optimal cell source for MSC-based cartilage repair would be. Moreover, cells have been implanted using various carriers, passages, and doses, which can introduce new variables. Finally, it is just recently that we are beginning to understand the paracrine "signaling," rather than "differentiating," role MSCs have *in vivo*.

In Asia, governing bodies have allowed products with an adequate safety profile to be permitted onto the market without potency testing. Cost-efficacy is assessed under postmarketing surveillance and clinical effectiveness is assigned to the judgment of patients, providers, and payers. The challenge to the regenerative medicine community is now to unite standards of validity and utility in an international and collaborative way.

In the cartilage regeneration field, recent initiatives to launch a registry may provide a comprehensive global assessment, and, thus, improve implementation. Coordination between the local

regulatory committees, the European Medicine Agency in Europe, and the FDA in the United States, is of utmost importance. Meanwhile, the exciting field of regenerative medicine will continue its development to provide durable and cost-effective solutions for musculoskeletal injuries.

CONFLICT OF INTEREST

D.S. is a consultant for VeriCel, Smith & Nephew and Cartiheal. A.K. is a consultant for Arthrex. As Deputy Editor-in-Chief for *Clinical Pharmacology & Therapeutics*, Andre Terzic was not involved in the review or decision process for this paper.

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