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Review article

Concepts in regenerative medicine: Past, present, and future in articular cartilage treatment

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ABSTRACT

Regenerative medicine is emerging with great interest and hope from patients, industry, academia, and medical professionals. Cartilage regeneration, restoration, or repair is one of the prime targets that remains largely unsolved, and many believe that regenerative medicine can possibly deliver solutions that can be widely used to address the current gap(s) in treatment. In the United States, Europe, Australia, and India the regulation of regenerative based treatments has become a big debate. Although the rules and regulations remain unclear, clinicians that are interested should carry-on with the best available guidelines to ensure safety and compliance during delivery in clinical practice to avoid regulatory infraction. Many have made significant investment of time, resources, and facilities in recent years to provide new regenerative treatment options and advance medical care for patients. Instead of reinventing the wheel, it would be more efficient to adopt currently accepted standards and nomenclature borrowed from transplantation science, and cord blood storage industries. The purposes of this article are to provide some historical background to the field of regenerative medicine as it applies to cartilage, and how this field has developed. This will be followed by a separate discussion on regulatory oversight and input and how it has influenced access to care. Furthermore, we discuss current clinical techniques and progress, and ways to deliver these treatments to patients safely, effectively, and in a cost sensitive manner, concluding with an overview of some of the promising regenerative techniques specific to cartilage.

1. Introduction

Regenerative medicine is emerging with great interest and hope from patients, industry, academia, and medical professionals alike. The opportunity to cure un-curable or difficult to treat disorders and diseases captures and fuels momentum by most stakeholders to provide solutions for the today and the future. Cartilage regeneration, restoration, or repair is one of the prime targets that remains largely unsolved for which regenerative medicine can be a solution and address the current gap(s) in treatment.

The definition of regenerative medicine is the treatment of medical conditions that harnesses the human body's inherent ability to regenerate a tissue at the level of cellular or organ structure, that foster cellular communication, translation, organ system refurbishment, and result in overall organism well-being. Strategies of treatment include healing response, genetic influence/modification, external stimulus, cellular signaling, exogenous augmentation. Therefore, organ and tissue engineering will be excluded, however will include regeneration that may or may not include cellular transplantation.

Although it may not seem apparent, the underlying purpose of regenerative medicine may not be just for curing a disease, but for the perfection of human organism, and possibly physical immortality.[1] However, standing in the way of progress in the developed world are regulatory barriers that may or may not be appropriate for these treatments. The rapid expansion of the field has outpaced regulation and existing rules have provided little guidance for both clinicians and scientists on the best way to proceed. Unfortunately, organization in the required processes for determining who are good candidates for treatment, candidate

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evaluation and initiation, informed consent, sample collection and handling, cellular processing, standard operating procedures (SOPs), treatment administration, outcomes, reporting, and adverse events are still being established leaving the regulators in a precarious position of balancing the protection of patients between clinical progress.

The purposes of this article are to provide some historical background to the field of regenerative medicine as it applies to cartilage, and how this field has developed. This will be followed by a separate discussion on regulatory oversight and input and how it has influenced access to care. Furthermore, we discuss current clinical techniques and progress, and ways to deliver these treatments to patients safely, effectively, and in a cost sensitive manner, concluding with an overview of some of the promising regenerative techniques specific to cartilage.

2. History of regenerative medicine-cartilage

Although we may not recognize, regenerative medicine as far as addressing cartilage of synovial joints is concerned has dual origins. Non-operative treatment finds its foundations back to 1930s with a Philadelphia general surgeon' self treatment of a thumb injury with "proliferative" or sclerosing agents and later the treatment of painful hypermobile joints.[2] Shortly after, in 1940s surgical treatment to address osteoarthritis was described with the extensive debridement of osteoarthritic knee joints as described by Magnuson.[3] The procedure involved removal of synovium, loose cartilage, and osteophytes thus prompting a "healing response", and this procedure was used for many years until supplanted by formal arthroplasty. In 1950s again, on separate fronts regenerative promoting procedures were described. In America, Hackett (1956) thought that peripheral joints that became painful were a result of axial instability and referred neural input with loss of muscular and ligamentous control, and has laid the foundation for prolotherapy in the treatment of arthritic joints.[4] Almost simultaneously in the United Kingdom, Pridie expanding on the previous work of Magnuson, at the British Orthopaedic Association (1959) and presented a technique of closely spaced multiple drilling of knee arthritic articular cartilage defects to promote a regenerative response. Although complete clinical outcomes were not presented initially, Insall in 1974 for 60 patients, the procedure was successful in selected patients.[5,6] Microfracture is another healing response treatment, but was created to treat full-thickness cartilage injury in contrast to arthritis as Pridie drilling was intended. The initial technique was described in 1994,[7] however the clinical results from treatment were reported from 1981, by Steadman et al. much later with average 11-year follow-up demonstrating clear clinical utility.[8] Other investigators eventually reported their results which revealed smaller lesions located on the femoral condyles, and trochlea appeared to be the best to treat with this method. Large, multi-focal, and/or patellar lesions still presented a treatment dilemma. Around the same time, another method of cartilage repair called autologous chondrocyte implantation and the use of bone marrow derived cells to regenerate knee articular cartilage was published.[9,10] The first technique involved culture expansion of knee articular chondrocytes, re-implantation below a periosteal patch.[9] The second technique specifically used culture expanded bone marrow derived cells[11] (CE-BMDC) that demonstrated excellent short-term safety, and efficacy to autologous chondrocytes for focal cartilage lesions.[12] Concurrently, identification, characterization and mechanism of mesenchymal stem cell[13] was described by Caplan who coined the term "MSC." Many describe him as the "Father of Mesenchymal Stem Cell" and who reported that perivascular adluminal cell or pericyte surrounds all blood vessels, and that all pericytes are MSCs.[14] Later, cell augmented marrow stimulation procedures (microfracture and/or drilling) of both focal lesions as well as arthritis with concentrated bone marrow aspirate (BMAC), adipose-stromal vascular fraction (A-SVF), CE-BMDSC, culture expanded-adipose derived stem cells (CE-ADSC), peripheral blood stem cells (PBSC), and many other sources.[15,16] As the drive to improve continued, and patient desires for minimally invasive procedures, the age of Regenerative Injection Therapy (RIT) was born, largely by the advances of Linetsky who coined the term and is considered to be the originator of "Regenerative Injection Therapy or RIT".[17,18] Dr. Linetsky continued the initial work of prolotherapists (Gedney, Hackett, and Hemwall).[19,20] This progression consisted of injecting all sorts of agents that induce a biological response, including: dextrose, sodium bicarbonate/calcium gluconate, hyaluronic acid, platelet rich plasma (PRP), bone marrow aspirate concentrate (BMAC), nano or micronized fat, adipose-stromal vascular fraction (A-SVF), culture expanded meschymal stem cells (CE-MSCs) both allogenic as well as autologous from a multitude of sources are becoming more commonplace.[16] The aggregate number and quality of studies are steadily improving, it is no doubt that the application of the cells are safe[10,12,21,22] and efficacious.[16]

3. Regulatory implications facing cartilage regenerative medicine

In the United States, Europe, Australia, and India the regulation of regenerative based treatments has become a big debate.[23–28] Although the rules and regulations remain unclear, clinicians that are interested should carry-on with the best available guidelines to ensure safety and compliance during delivery in clinical practice to avoid regulatory infraction.[29] While ill-defined regulation encourages experimentation and novel clinical application, efficacy and patient safety concerns are a real concern.[30] Additionally, strict regulation strangles innovation and clinical implementation yet provides the proof of safety and efficacy, prior to routine use. However, put into perspective, in consideration of the bulk of regenerative medicine experimental and clinical work, that involves interspecies organ transplantation, genetic modification,[31,32] to ultimately create human bodies in bioreactors[1] (Fig. 1) in comparison at worse to the clinical use of culture expanded autologous cells stem cells with a long-term proven safety record is curious.

The practice of medicine requires physicians to constantly innovate and update to improve patient care. On the surface, the benefits of strict regulation providing patient safety and efficacy seem worthwhile however; due to the individual and personalized nature of these treatments, it is quite difficult to establish protocols and procedures for treatments with conclusive and generalizable evidence. Currently, within the United States, the Food and Drug Administration (FDA) utilizes an outdated and inappropriate pathway for the ability of clinicians to utilize stem cell therapies in humans that is more akin to approval processes for conventional pharmaceuticals (Fig. 2). To date there has not been any stem cell product widely available despite extensive clinical trials.[33] After defining case upheld in the Washington, D.C. US Court of Appeals in 2014,[34] the basic conclusion is that an individual's cells are drugs, and only cellular products that have made it through exhaustive clinical trials after investigational new drug application (IND) can be used, and only after a biologic license is granted. There appears to be great coordination between the FDA and the European Medicines Agency (EMA) and current outstanding draft guidance(s) under debate pertaining to 21 CFR 1271 for same day procedures in the USA include: homologous use, surgical exemption, use of adipose tissue, minimal manipulation; and EU Regulation 1394/2007 classification of advanced medicinal therapeutic products (ATMPs)-homologous use, minimal manipulation, and hospital exemption.[35–38] The basis for intervention has been

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