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Orthobiologics: Where are we Now?

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Mini Review

Over the last decade, the demand for minimally invasive treatments of musculoskeletal injuries has markedly increased. Recent advances in technology and developments in scientific understanding have created a myriad of new opportunities to meet this demand. One particular area which has experienced a growing volume of research is called orthobiologics. Orthobiologics is defined as any treatment that utilizes the body's native cellular components to promote healing of damaged or diseased tissues [1,2]. Currently, there are 4 generations of orthobiologics including: Hyaluronic acid (HA), platelet-rich plasma (PRP), bone marrow concentrate (BMC), and adipose-derived mesenchymal stem cells (aMSC). Although the current landscape of orthobiologics can be classified by 4 generations, the field as a whole is in the preliminary stages. Continued research and collaboration is needed to expand our understanding of these treatments and shape its future direction.

Hyaluronic acid (HA) is widely considered the first generation of orthobiologics. HA is a naturally occurring protein in humans that has many functions, most importantly acting as an intra articular lubricant, working to reduce friction in synovial joints. Studies have shown overall HA concentration in synovial fluid to decrease with Osteoarthritis[3], with a resultant shift from high molecular weight to low molecular weight variants. In addition, high molecular weight variants have been shown to be superior to low molecular weight variants for chondroprotection in joint osteoarthritis [3]. In theory, the administration of intra articular HA increases the synovial fluid concentration of HA, to possibly prevent symptoms of pain and decrease further joint degeneration [3]. Hyaluronic acid has been shown to bind to cluster of differentiation 44 (CD 44), which inhibits the pro-inflammatory effects of interleukin-1beta, resulting in down regulation of many MMPs associated with cartilage degradation [4,5].

Several clinical trials have shown HA to effectively treat pain associated with OA [6], while also demonstrating a superior safety profile when compared to continuous NSAID use for pain control in OA [7-9]. In addition, OARSI suggests "good" level of evidence for the treatment of OA with intra articular hyaluronic acid. Although HA has been primarily been used for large joint osteoarthritis, there is a small amount of research investigating its application for spinal pathologies, including facet mediated low back pain, and intradiscal injections of HA-based hydrogels for degenerative disc disease [10,11]. Platelet Rich Plasma (PRP)was first used for open heart surgery in 1987 [12] but has since emerged as the second generation of orthobiologics for musculoskeletal pathology. PRP is extracted from a patient's own blood supply. Venous blood is drawn from the patient and centrifuged in order to separate the blood into multiple layers, including the buffy coat, which contains the largest concentration of platelets. The buffy coat is removed from the processed venous blood and re-injected into various treatment areas [13]. The proposed therapeutic benefit of PRP is based in its ability to stimulate an inflammatory cascade and initiate a healing response through release of growth factors from its alpha granules, including transforming growth factor beta (TGFbeta), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epithelial growth factor (EGF) [13,14]. More recent theories of PRP's mechanism suggest that intra articular application may potentially alter the entire joint environment via the signaling cascade, creating a more advantageous inflammatory environment for healing [15].

Most of the research for PRP consists of heterogenous, small case series, however some larger randomized controlled trials have demonstrated its use in areas such as chronic tendinopathies [16,17] and knee osteoarthritis [18]. In addition, its application for facet mediated low back pain and degenerative disc disease have also started to be researched [19,20]. Some early studies

have also started to examine the combination of PRP with other orthobiologic generations [21-23], as well as various treatment protocol sequences [24], with significant benefits illustrated. However, in all areas of PRP research, uniformity of PRP classification has been lacking, and recent development of PRP classification systems such as the PLRA [25] and MARSPILL [26] have attempted to provide more clarity and standardization across the field, as well as unify research efforts in the future.

The third generation of orthobiologics is bone marrow concentrate (BMC), which consists of a milieu of mesenchymal stem cells (MSCs), hematopoietic cells, platelets, and cytokines noted for possessing anti-inflammatory, immunomodulatory, and chondrogenic properties [27]. While the mechanism is not known, it is thought that BMC either induces differentiation and proliferation of resident stem cells, or possesses innate chondrogenic potential [27]. Procurement of BMC includes aspiration of bone marrow from the patient, usually at the posterior superior iliac crest under fluoroscopic or ultrasound guidance. In a similar manner to PRP, the aspirate is then centrifuged, and specific layers are extracted for injection. Although much of the early research has been mixed, some preliminary studies have demonstrated significant patient safety and efficacy with joint osteoarthritis [28-31]. Research efforts have also been directed towards intradiscal applications in degenerative disc disease, through an ongoing clinical trial called the CASCADE trial, examining the use of BMC with and without HA for discogenic low back pain [32].

The newest and fourth generation of orthobiologics is known as lipoaspirate/adipose derived mesenchymal stem cells (aMSCs). Lipoaspirate is obtained inlarger amounts with less invasive techniques via local anesthesia and vacuum-assisted lipectomy to the posterior superior buttock or lateral thigh. In contrast to PRP and BMC, lipoaspirate involves low speed centrifugation or settling of the suctioned adipose tissue for several hours without centrifugation [30]. Similar to BMC, processed lipoaspirate has illustrated chondrogenic, osteogenic, adipogenic, myogenic, and neurogenic differentiation in the presence of certain induction factors [33,34]. Some research has illustrated that aMSCs actually possess larger total numbers of MSCs, however data is mixed as to whether aMSCs have equivalent osteogenic potential as BMC [35,36]. Early research suggests that aMSCs exhibit an anti-inflammatory effect on chrondrocytes and synoviocytes in patients with Osteoarthritis [37], however significant research is needed in this generation of orthobiologic.

Orthobiologics is a vastly expanding field within musculoskeletal medicine, currently characterized by 4 generations: hyaluronic acid, platelet rich plasma, bone marrow concentrate, and adipose derived mesenchymal stem cells. Future generations of Orthobiologics are currently being developed, most notably, amniotic tissue as an allogeneic source for mesenchymal stem cells [38,39]. Although applications within each generation continue to expand, significant research and collaborative efforts are needed to increase our understanding of potential therapeutic benefits and further study the cellular constituents of each orthobiologic.

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