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Amniotic Tissue Modulation of Knee Pain—A Focus on Osteoarthritis

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Abstract

The use of intra-articular therapies as sources of growth factors, anti-inflammatory mediators, and medicinal signaling cells for osteoarthritis (OA) is rapidly evolving. Amnion, chorion, amniotic fluid, and the umbilical cord are distinct placental tissues that have been investigated for use in OA. Amniotic membrane (AM) synthesizes a variety of growth factors, cytokines, and vasoactive peptides that modulate inflammation. In addition, they contain amniotic epithelial cells and amniotic mononuclear undifferentiated stromal cells, which have chondrogenic and osteogenic differentiation capacity. AMs are also rich sources of hyaluronic acid and proteoglycans, which could play a role in the potential therapeutic relief of OA. Currently, there are several commercially available formulations of AM that differ based on content as well as how they were preserved. Understanding the processing of amniotic tissue is important because of their distinct mechanical and biologic effects of preservation on AM grafts. To date, there have been two preclinical and only one clinical study on the use of AM for OA, which show promising results. Many high level of evidence clinical trials are currently underway investigating the use of AM of OA. Future basic science and clinical research is warranted to better understand the anti-inflammatory and chondroregenerative properties of amniotic tissue and to determine clinically what amniotic tissue product is most efficacious for symptomatic OA.

Keywords

cartilage - osteoarthritis - amniotic suspension allograft - amniotic membrane - amniotic fluid

The placenta is a complex structure integral for fetal development. Over the past two decades, the human placenta has garnered significant interest as a source of multipotential cells, some of which may be medicinal signaling cells (MSCs).[1] MSCs are multipotent cells that can self-renew and differentiate into multiple tissues including bone, cartilage, muscle, adipose, and connective tissue.[2] In addition, these cells secrete bioactive immunomodulatory and trophic factors at sites of injury and disease to help direct native tissue-specific resident stem cells to participate in tissue repair and regeneration.[3] MSC was originally an abbreviation for mesenchymal stem cells; however, Caplan recently coined the term "medicinal signaling cells" to de-emphasize the words "stem cells," which he felt were often misrepresented. The term "medicinal signaling cells" places more emphasis on the typical role they play, which is often signaling or directing other cells rather than differentiating into other cell phenotypes.[3] Several adult sources of MSCs have been identified including bone

marrow,[4] adipose tissue,[5] and synovial tissue.[6] The human placenta contains several sources of MSCs that are known to have greater differentiation plasticity and higher proliferative capacity compared to adult stem cells.[7] [8] [9] In addition, placental-derived tissues are a rich source of growth factors, cytokines, and extracellular matrix (ECM) that may be beneficial in tissue regeneration and repair ([Table 1]). These properties, in addition to the ease of isolation of cells and the availability of the placenta as a discard tissue, make placental-derived tissues an attractive and less controversial source of cells that may be beneficial in regenerative medicine.

Table 1 Placental-derived tissues

Abbreviations: AECs, amniotic epithelial cells; AMSCs, amniotic mononuclear undifferentiated stromal cells; CMSCs, chorionic mesenchymal stem cells; MSC, medicinal signaling cell.

Anatomy and Function of Placental-Derived Tissues

Amnion, chorion, amniotic fluid, and the umbilical cord (UC) are distinct placental tissues that have been investigated for use in orthopaedic surgery. The UC is an extraembryonic structure that connects the mother and fetus. It serves as a conduit for blood, nutrients, and gas exchange between the mother and fetus. The fetal membranes are the chorion and amniotic membrane (AM), which together encapsulate the amniotic cavity.

The chorion is the outer layer of the fetal membranes that is in direct contact with maternal tissue. Composed of both mesenchyme tissue and the trophoblast layer, the chorion contributes to placenta growth and contains chorionic villi. The chorionic villi are in the trophoblast tissue and are the site of blood, oxygen, and nutrient exchange between the fetus and mother.

The AM is the avascular and aneural inner layer that is in direct contact with fetal tissue. During development, the AM forms from the trophoblast layer to create three distinct components that distinguish the amniotic cavity from the chorion: the epithelial layer, basement membrane, and avascular mesenchymal tissue.[10] The epithelial layer is a single layer of tightly packed epithelial cells with microvilli that are integral in cell transport and secretion. This layer is in direct contact with amniotic fluid and is thought to serve as a barrier to adhesion during development. The amniotic basement membrane is the thickest basement membrane in all human tissues and anchors the epithelial layer. The mesenchymal tissue contains three layers: compact, fibroblast, and spongy layers. The compact layer is an acellular layer composed of type I and type III collagens as well as fibronectin. The fibroblast layer is composed of type I and type III collagens and provides structural integrity to the AM. The spongy layer is loosely organized with type III collagen and separates the AM from the chorion. It serves as a rich source of proteoglycans and glycoproteins, including hyaluronic acid (HA).

The AM has several functions. It is intricately involved in regulating amniotic fluid pH by modulating water and soluble material transport for the fetus.[11] In addition, the AM synthesizes a variety of growth factors, cytokines, and vasoactive peptides. Many growth factors are produced by cells of the AM including, but not limited to, basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), keratinocyte growth factor, hepatocyte growth factor, noggin, nerve growth factor, brain-derived neurotrophic factor, transforming growth factor-β (TGF-β),[12] interleukin 1 receptor antagonist (IL-1Ra), interleukin 10 (IL-10), insulin-like growth factor 1,[13] and transforming growth factor-α (TGF-α).[12] [13] [14] [15]

Cells in Placental-Derived Tissues

AM is harvested from the human placenta after childbirth from volunteers who consent to the use of their placental tissue. It contains two forms of stem cells: amniotic epithelial cells (AECs) and amniotic mononuclear undifferentiated stromal cells (AMSCs).[16] AMSCs are derived from embryonic mesoderm and can be isolated during the first, second, and third trimesters. To isolate AMSCs, AM tissue is dissected from maternal-derived tissue and then digested with trypsin to remove AECs. The remaining mesenchymal cells are then released with collagenase and/or DNAse.[16] Amniotic tissue typically yields 1 million AMSCs/g of tissue. AMSCs can differentiate into all three germ layers. Multiple surface and molecular markers of pluripotent stem cells are expressed by or found on AMSCs including CD105, CD90, CD73, CD44, octamer-binding protein 4 (OCT-4), E-cadherin, and human leukocyte antigen (HLA)-A,B,C.[1] [17] [18] CD49d expressed on AMSCs differentiate AMSCs from AECs.[19]

AECs are derived from maternal tissue and also can differentiate into mesoderm, endoderm, and ectoderm.[20] AECs are isolated by stripping the AM from the chorion and digesting it with digestive enzymes such as trypsin to isolate the epithelial cells.[20] [21] Many different surface and molecular markers of pluripotent stem cells have also been identified on or expressed by AECs including OCT-4, SRY-related HMG-box gene 2 (*SOX-2*), Nanog, stage-specific embryonic antigens (SSEAs 3 and 4, HLA-A, HLA-B, HLA-C, E-cadherin, CD90, CD73, CD44, CD13, CD10).[1]

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Both chorionic villi and membrane contain MSCs.[22] [23] MSCs from chorion (CMSCs) can be isolated from both first- and third-trimester chorions via mechanical removal, enzymatic removal of the trophoblastic layer with dispase and digestion of the membrane with collagenase. The yield of MSCs can range from 10 to 40,000 cells/cm^2.[18] [24] Chorion-derived MSCs have great differentiation potential with adipogenic, chondrogenic, osteogenic, skeletal myogenic, and neurogenic differentiation reported.[25] In comparison to CMSCs, AMSCs have mesenchymal and epithelial characteristics, which is a sign of their multipotentiality. CMSCs, on the contrary, are more primitive and metabolically quiescent.

Biologic Properties of Amniotic Tissue

AM expresses many anti-inflammatory proteins. Hao et al found both AECs and AMSCs express both (IL-1Ra and IL-10.[26] IL-1Ra competes with IL-1 to bind to the IL-1 receptor to block inflammatory processes initiated by IL-1. IL-10 is a broader spectrum anti-inflammatory cytokine that inhibits production of multiple proinflammatory cytokines and proteins including IL-1, tumor necrosis factor (TNF)-α, and matrix metalloproteinases (MMPs). AM also activates anticatabolic pathways through multiple mechanisms, including promoting the expression of multiple forms of tissue inhibitors of metalloproteinases (TIMPs) including TIMP-1 and TIMP-2. TIMPs are protease inhibitors that inhibit MMPs, which are endopeptidases that degrade ECM proteins.

Macrophages are well known to exhibit different phenotypes (both proinflammatory and anti-inflammatory) in vivo and in vitro during healing and tissue regeneration.[27] Typically, proinflammatory macrophages accumulate during the early stages of healing, while anti-inflammatory macrophages accumulate later. AM tissue can modulate this macrophage polarization. Witherel et al found that AM tissue inhibits TNF, which may minimize prolonged inflammation.[28] Amniotic tissue also downregulates proinflammatory cytokines TNF, CCL5 (RANTES), and CCR5 (CD195), leading to a diversion of macrophages from the proinflammatory phenotype to the anti-inflammatory phenotype.[28] [29]

Early Clinical Use of Amniotic Tissue

Historically, AM was used as a scaffold for complex tissue regeneration for skin disorders such as burns, ulcers, and wounds. The first use of AM was in 1910, when it was used to treat a skin defect.[10] The clinical advantages of AM are its anti-inflammatory properties, low immunogenicity, promotion of wound healing, and fibrosis inhibition. Today, AMs continue to be used as biologic dressings for acute and chronic nonhealing or infected wounds, burns, and ulcers. Several studies have found that AMs improved and accelerated the healing process of chronic wounds.[30] [31] Additionally, AMs have also been used in ophthalmology to treat corneal surface injuries.[32]

Placental-derived tissue has only recently been explored in orthopaedics for tissue regeneration. Current areas of investigation include plantar fasciitis, ligament and tendon healing, cartilage restoration, and osteoarthritis (OA). In vivo studies have found that AM may improve the mechanical properties of Achilles tendon repairs and increase collagen production.[33] [34] Other studies have found that after tendon repair, AM may reduce fibrosis and adhesion formation.[35] For cartilage regeneration, AMSCs can be induced to a chondrocyte phenotype in the presence of a chondrogenic medium and bone morphogenic protein (BMP)-2 or BMP-7.[36] [37]

Seven clinical studies on the use of AM for orthopaedic pathology have been published. Two studies are published on the use of amniotic suspension allograft (ASA) as an augment to spinal arthrodesis procedures.[38] [39] In 2016, Sclafani et al published a retrospective review of 87 patients who underwent either an anterior or posterior lumbar interbody fusion. The authors found that patients had significant improvement in pain and disability index scores at 1 year, with older patients showing a greater improvement. Interpretation of the results is limited due to a lack of a control group, but no adverse events were reported. Nunley et al published a retrospective study with a prospective computed tomography scan to evaluate fusion rates, looking at 72 patients who underwent interbody fusion and found high fusion rates and no adverse events in a complex patient set where more than 85% of the patients had at least one serious comorbidity. In 2015, Anderson and Swayzee published a series of 101 patients who underwent ankle arthroscopy with microfracture for treatment of osteochondral lesions of the talus. Among those 101 patients, 54 had augmentation with AM suspension allograft. When compared with those patients who did not have augmentation, patients whose surgeries were augmented with AM had improved pain and functional outcome scores at both early and 24-month follow-ups.[40] Werber conducted a prospective study of 44 patients who failed 6 months conservative management for chronic plantar fasciitis and Achilles tendinosis and received an injection of cryopreserved human AM and amniotic fluid.[41] At the 12-week follow-up, all patients had improved pain scores as measured by visual analog scale and there were no adverse events. Two additional randomized controlled trials (RCTs) have been published on the use of micronized dehydrated human amnion/chorion membrane (μ-dHACM) and cryopreserved AM for treatment of refractory plantar fasciitis, each with no reports of adverse events.[42] [43]

Amniotic Tissue for Treatment of Osteoarthritis

OA is a chronic, costly, and debilitating condition that historically has been attributed to mechanical degeneration. Many attributed the pathophysiology of OA to altered mechanics due to a decrease in the resiliency of OA cartilage to compression, axial, or shear loading.[44] This is in part due to a loss of proteoglycan content, increased lesion formation, calcification of the ECM, and hypertrophic differentiation of chondrocytes.[45] However, recent evidence has implicated inflammation and alterations in cartilage metabolism in the pathogenesis of the disease.[46] [47] Increased catabolism and decreased anabolism lead to a breakdown of cartilage ECM and increased inflammation in synovial fluid and tissue. The concentration of important synovial fluid cytokines such as IL-1α, IL-1β, IL-18, and TNF-α are associated with the severity of OA.[48] [49] In OA synovium, there is a decline in IL-1Ra production, leading to increased IL-1 levels that may be a result of excess nitric oxide produced in OA.[50] Stannus et al found that synovial fluid levels of IL-6 and TNF-α are also associated with the prevalence of radiographic joint space narrowing.[51] Many other cytokines (e.g., IL-6, IL-13) and biologic markers including C-reactive protein (CRP), complement, MMPs, chemokines (e.g., CX3CL1), and adipokines (e.g., leptin, adiponectin) have been implicated in the pathogenesis in OA and remain an area of investigation. To date, there are no disease-modifying OA drugs that are proven to modulate these metabolic and inflammatory processes and prevent progression of the disease.

The use of intra-articular therapies as sources of growth factors, anti-inflammatory mediators, and potentially MSCs for OA is rapidly evolving. These nonsurgical treatments aim to slow the disease process, reduce pain, and increase function. MSCs have garnered significant interest due to their chondrogenic potential and promise for tissue regeneration.[52] In addition, MSCs may also have significant trophic and immunomodulatory effects on OA.[4] In a double-blinded randomized study of cultured allograft MSCs to promote meniscal regeneration after partial meniscectomy, Vangsness et al found no significant meniscal regeneration but did find significant pain reduction for up to 2 years in the subset of patients with mild OA.[53] The AM is a metabolically active tissue that has also garnered recent interest in cartilage research for its anti-inflammatory and chondroregenerative potential.[54] [55] AMs have several functions that make them a promising therapy for OA. AMs contain anti-inflammatory factors and upregulate several anti-inflammatory pathways, such as IL-10 and IL-1Ra, which may help alter OA inflammation.[26] Growth factors identified in AM include IL-4; IL-6; IL-8; IL-10; TIMP-1, -2, and -4; EGF; TGF-α; TGF-β, bFGF; and platelet-derived growth factor (PDGF)-AA and -BB.[56] [57] In addition, MMPs are inhibited by AMs through the up-regulation of TIMPs. AMs are also rich sources of HA and some proteoglycans, which could play a role in the potential therapeutic relief of OA.[58] HA-binding proteins (HABPs) have also been identified in AM. HABPs are biologically active proteins that attach directly to HA and may play an important role in the anti-inflammatory and antiscarring properties of AM.[59] Other ECM components identified in AM include fibronectin, laminin, and type I and type IV collagens.[60] Other chondroprotective growth factors expressed by AMs include PDGF and FGF-18, which have been implicated in chondrocyte proliferation and hypertrophy.[61]

Currently, there are several commercially available formulations of AM ([Table 2]). AM is isolated from human placentas that are donated under informed consent typically after cesarean sections. Donors are tested and confirmed to be free of infectious diseases including hepatitis B, hepatitis C, syphilis, human immunodeficiency virus, and human T-lymphotrophic virus. Fresh AM is stored at 4°C after being processed with a phosphate-buffered saline wash with penicillin and streptomycin.[62] [63] However, due to concerns regarding infection rates as high as 8% and the need to transplant fresh grafts with a very short period after harvest, fresh AM has not been extensively used clinically.[64] [65] Most commercial products are forms of preserved AM.

Table 2 Commercially available amniotic tissue allograft products

Abbreviation: dHACM, dehydrated human amnion/chorion membrane.

[a] *Preclinical study results of Willet et al[70] available in [Table 3].*

[b] *Preclinical study results of Raines et al[45] available in [Table 3].*

The three major forms of preservation of amniotic tissues are cryopreservation, lyophilization (freeze drying), and low-heat dehydration. Lyophilization dehydrates amniotic tissue and removes water through freeze drying. After freezing the tissue, ambient pressure is dropped so that sublimation can occur, allowing frozen water to convert directly from solid to gas.[66] Lyophilization removes the live cellular component of AM, but still maintains the rich supply of growth factors and its ECM structure. Cryopreserved cellular human amniotic allografts contain the AM and cells from the amniotic fluid. Cryopreservation steps are completed to freeze and allow storage of amniotic grafts at −80°C using a cryoprotectant such as dimethyl sulfoxide.[66] Importantly, preservation has no influence on the integrity of the basement membrane, ECM, and growth factors, all of which play a role in the anti-inflammatory, cell adhesion, and cell proliferation effects of AM.[67] However, there are other important mechanical and biologic effects of preservation on AM grafts. Niknejad et al found that

both forms of preservation led to decreased levels of type I and type III collagens and thinning of the compact layer when compared with fresh grafts.[66] In addition, both preservation techniques lead to lower tensile strength and maximal loads to failure compared with fresh AM grafts. When directly comparing lyophilized grafts to cryopreserved grafts, lyophilized amniotic grafts are thinner and more fragile, but have greater host cell adhesion and viability.[66] A third processing technique of amniotic tissue is dehydration with low heat. In dehydration, water content is removed, collapsing the ECM, resulting in a decrease in matrix thickness and decreased protein content compared with cryopreserved amnion.[68] In addition, low heat dehydration may reduce HA content and other growth factors and cytokines.[69] However, the advantage of dehydrated amniotic tissue is that it can be stored at ambient temperature allowing products derived from this processing technique to be stored on the shelf. Dehydrated amniotic tissue-based products also have a long-shelf life similar to lyophilization.

Preclinical Studies on Amniotic Tissue for Osteoarthritis

To date, there are two preclinical studies published on the use of amniotic tissue for OA ([Table 3]). In 2014, Willet et al used a Lewis rat OA model using medial meniscal transection and randomized rats to receive either μ-dHACM or saline 24 hours postsurgery.[70] An additional group of Lewis rats did not have their medial meniscus transected but received an intra-articular injection of saline or μ-dHACM. Study animals were euthanized at 3 or 21 days postinjection and histology, synovial fluid, and EPIC-μCT (equilibrium partitioning of an ionic contrast agent via microcomputed tomography) were analyzed. In surgically naïve rats, injection of μ-dHACM did not affect native cartilage as measured by histology (hematoxylin and eosin staining) and EPIC-μCT (cartilage volume, thickness, and attenuation). In surgical rats, those treated with μ-dHACM had significant reduction in cartilage damage including less erosions, cartilage attenuation, and focal defects on EPIC-μCT. Injection of μ-dHACM after surgery resulted in hypercellularity around the dHACM fragments at both 3- and 21-days postoperatively, with no cartilage damage compared with the saline injection rats. Most cytokine levels in the synovial fluid were below the limit of detection by enzyme-linked immunosorbent assay.

Table 3 Preclinical studies on amniotic tissue for osteoarthritis

Abbreviations: AM/UC, amniotic membrane/umbilical cord; μ-dHACM, micronized dehydrated human amnion/chorion membrane; OA, osteoarthritis; OARSI, Osteoarthritis Research Society International.

Raines et al used the same Lewis rat OA model with medial meniscus transection to study the effects of human cryopreserved, particulate AM/UC.[45] Rats were injected with either saline, 50 μg/μL AM/UC, or 100 μg/μL AM/UC 2 weeks following surgery and killed at either 1 week or 4 weeks after injection. At 1 week after injection, rats receiving AM/UC had significant reduction in lesion area and per cent lesion area on EPIC-μCT compared with saline. Rats who received 100 μg/μL AM/UC had increased cartilage thickness and volume at 1 week, and a significant reduction in lesion area and per cent lesion area at 4 weeks compared with both saline and 50 μg/μL AM/UC. There were no differences between the groups in synovial membrane inflammation; however, Osteoarthritis Research Society International histology grading of articular cartilage showed significant reduction in cartilage degeneration, calcified cartilage, and the total joint score of rats receiving AM/UC.

Lei et al as part of a review on dHACM allografts for orthopaedic tissue repair reported the influence of dHACM on HA synthase gene expression in OA and rheumatoid arthritis (RA) tissues.[71] Human fibroblast-like synoviocytes (HFLS) were isolated from normal synovium, osteoarthritic synovium, and rheumatoid arthritic synovium. After isolating HFLS from each type of synovium, the HFLS were treated with μ-dHACM allografts. After 3 days, HA synthase 1 (HAS1) and HAS2 gene expression was measured in addition to HA production. μ-dHACM promoted significant up-regulation of HAS1 and HAS2 gene expression over 3 days in both OA and RA tissues. They also found a significant increase in HA production in the RA tissue but not in OA tissue.

Clinical Studies on Amniotic Tissue for Osteoarthritis

While amniotic products have been widely used in other fields such as wound healing, their use in orthopaedics need to be further elucidated. Determining appropriate use in a new field requires understanding situations where the technology is effective, determining what product-specific factors determine success, and guiding future usage based on this information. For instance, platelet-rich plasma was used widely upon first adoption and now it is clear that low white blood cell (WBC) content is beneficial for arthritis, whereas the opposite is true for tendonitis. Though this information does not yet exist for amniotic products, there has been investigation into its use as an injectable for OA. Nevertheless, it is too early to comment on where amniotic products will fall in the paradigm of OA treatments, yet the suggestion is that they may participate in

every changing group termed "orthobiologics." As such, a future place in OA treatment algorithms is only at the level of conjecture. Current literature suggests that this treatment is safe and level 1 RCTs are underway to further describe its efficacy.

The only clinical study published on the use of AM for OA was an open-label pilot study of six patients published by Vines et al.[55] Patients with Kellgren–Lawrence grade 3 or 4 knee OA were candidates for the study. Subjects were injected with 2 mL of cryopreserved ASA, which contains both AM and amniotic fluid-derived cells. Patients were followed up at 1 week, 2 weeks, 3, 6, and 12 months postinjection. No adverse events were reported. Patient-reported outcomes including Single Assessment Numeric Evaluation, International Knee Documentation Committee, and Knee Injury and Osteoarthritis Outcome Score all improved at each time point, but statistical analysis was deferred due to the small sample size. Labs including WBC count, CRP, erythrocyte sedimentation rate, and an immunologic panel were taken at multiple time points; no concerning changes were identified. The results from this study, including the lack of adverse events and inflammatory reactions coupled with improved PROs at 12 months, led to the initiation of an RCT to compare cryopreserved human ASA to placebo and HA in patients with OA that is ongoing.

As of April 2018, there are nine ongoing or recently completed unpublished trials on amniotic tissue for OA registered on ClinicalTrials.gov ([Table 4]). There is significant variation in the delivery and processing of amniotic tissue utilized. In addition, outcome measures across studies vary greatly.

Table 4 Ongoing clinical trials on the use of placental-derived tissue for treatment of osteoarthritis published on ClinicalTrials.gov

Abbreviations: ELISA, enzyme-linked immunosorbent assay; HA, hyaluronic acid; HHS, Harris hip score; IGF, insulin-like growth factor; IHOT12, International Hip Outcome Tool 12; IL-1Ra, interleukin 1 receptor antagonist; K-L, Kellgren–Lawrence; KOOS, Knee injury and Osteoarthritis Outcome Score; mdHACMb, micronized dehydrated human amnion chorion membrane biologic; MMP, matrix metalloproteinases; OA, osteoarthritis; ROM, range of motion; SANE, Single Assessment Numeric Evaluation; SF-12, RAND 12-Item Short Form Health Survey; SMFA, Short Musculoskeletal Function Assessment Questionnaire; TGF, transforming growth factor; TNF, tumor necrosis factor (TNF)-α; VAS, visual analog scale; VR-12, Veterans RAND 12 Item Health Survey; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. TMP

Regulation of Clinical Use of Amniotic Tissue

The U.S. Food and Drug Administration (FDA) regulates cell and tissue products, including AM, under the Public Health Service Act and the Food, Drug, and Cosmetics Act. The Center for Biologics Evaluation and Research and Center for Devices and Radiological Health are the arms of the FDA that regulate all cell therapies. Through these centers, the FDA uses a three-tiered risk-based system to regulate human cells, tissues, and cellular and tissue-based products (HCT/Ps).[72]

The FDA recently issued a guidance document clarifying its current views on the regulatory classification of amniotic tissue products.[73] Amniotic tissue products are regulated as either HCT/Ps with limited oversight (Section 361) or HCT/Ps that require extensive regulation as biologics and drugs (Section 351). To qualify as an HCT/P that is regulated under Section 361, the product must be used for homologous purpose, be no more than minimally manipulated, and cannot be combined with other cells or tissue except water, sterilizing or preserving or storage agents. The HCT/P must also have no systemic effects. Fresh or dried AM packaged as a sheet is considered an HCT/P regulated under Section 361 if it is used as a physical barrier or covering, including to offer protection from the surrounding environment. Other uses of AM are considered nonhomologous and thus are regulated under Section 351. Seeding of AM with allogeneic cells is considered more than minimal manipulation, thus qualifying those products for regulation under Section 351. HCT/Ps regulated under Section 351 require formal premarket approval from the FDA that can involve submitting a New Drug Application (NDA), an Investigational NDA (IND), or a Biologics License Approval (BLA). This process is lengthy, expensive, and often requires clinical trials to establish product safety, potency, efficacy, and stability.

Given that the recently issued guidance could change the previously understood classification of some tissue products, the FDA has indicated that it will exercise enforcement discretion for a period of 36 months to allow manufacturers of amniotic tissue products already on the market to transition those products to the correct classification. The FDA will not apply this discretion where the product or its application has reported safety concerns or significant potential safety concerns. Several manufacturers of amniotic tissue products have taken steps to pursue the requisite IND or BLA approval for OA applications. One, MiMedx, Inc. (Marietta, GA), has already submitted an IND for its AmnioFix product for OA and been granted Regenerative Medicine Advanced Therapy (RMAT) designation by FDA for this product. RMAT designation reflects a

determination by FDA that a regenerative medicine product is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and that preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. RMAT designation offers certain procedural advantages in the FDA approval process designed to speed the approval of designated products.

Conclusion

Amniotic tissue products are biologically active tissues that are rich sources of MSCs, cytokines, HA, and growth factors that may be beneficial in the treatment of OA. Different processing techniques from cryopreservation to dehydration alter the mechanical and biological properties of AM that should be considered when using AM clinically. Future basic science and clinical research is warranted to better understand the anti-inflammatory and chondroregenerative properties of amniotic tissue and to determine clinically what amniotic tissue product is most efficacious for symptomatic OA.

Conflict of Interest

C.P.H. reports no conflicts of interest related to the submitted work; he is a paid consultant for ExplORer Surgical, Inc., outside the submitted work. A.B.Y. reports research support from Organogenesis related to the submitted work; he is a paid consultant for JRF Ortho and has received research support from Arthrex, Inc., outside the submitted work. J.F. is a paid consultant for Organogenesis and has also received research support and royalties from there related to the submitted work; he is a paid consultant for Aesculap, Arthrex, Inc., Cartiheal, Ceterix Orthopaedics, Exactech, Moximed, Inc., Samumed, Inc., TRX Orthopedics, Inc., Vericel, ZimmerBiomet, Zipline Medical; he has received research support through 501(c) (3) non-profits from Active Implants, Arthrex, Inc., Ceterix Orthopaedics, Fidia Pharma, Histogenics, Moximed, Inc., Novartis, Inc., Vericel, ZimmerBiomet; royalties from Arthrex, Inc.; and stock/stock options from MedShape, Inc. and OrthoRegenerative Technologies, Inc., outside the submitted work.

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