Editorial Commentary: Amniotic Orthopaedic Biologics: There's Hope If We Avoid Hype

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Abstract: Amniotic products donated from mothers having live births have been in use for wound care and other medical uses for many years. Recent developments in regenerative sciences have suggested these products in solution or lyophilized forms may be useful for the treatment of inflammatory diseases such as chronic tendinopathies and osteoarthritis of joints. These products for these indications, however, are deemed human cells, tissues, or cellular or tissue-based products (otherwise known as HCTPs) in the "351" category, meaning that they need to have a biologic license to be marketed and sold in the United States, and to gain this license, one needs to go through the usual rigor of investigational new drug filing and phase 1, 2, and 3 trials to prove safety and efficacy. Although current clinical use of amniotic solution and lyophilized products is on hold through this study period, both basic science and clinical trial studies are building a convincing set of data that suggest broad possibilities for their uses in the future. To date, both animal and human studies have shown that a single injection of amniotic suspension allograft is safe, has not elicited any significant immune response, and has been shown to be effective in several prospective studies and at least one well-controlled randomized controlled human study for knee osteoarthritis when compared with both hyaluronic acid and placebo saline. Proteins in these harvested and processed tissue allografts are anti-inflammatory, anticatabolic, and proanabolic. Appropriate caution by the Food and Drug Administration in granting licenses for these indications should not dissuade basic scientists and physicians from pursuing further research into these interesting products.

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Recently, the Food and Drug Administration's (FDA's) exclusionary period expired for new regenerative products considered "351" products, or those requiring a biologic license. During this original 2-year period, then elongated because of COVID-19 virus, existing allograft products such as those from amnion, chorion, and placental products, as well as other "regenerative products" were allowed to continue to be sold, as long as the company producing them registered with the FDA to determine whether they qualified for "361" status due to minimal manipulation and several other stipulations. Since amniotic suspension allograft, as well as lyophilized amniotic products are more than minimally manipulated and their use nonhomologous, it has been clear from the beginning of this process that these allogeneic products would require a biologic license (BLA). Many of us in the field had hoped that companies that had been selling the product and had proven its safety—once registered and having applied for an IND—would be able to continue to market the product during their phase 2 and 3 study enrollment periods, but that has not happened. Therefore, as of June 1, 2021, these products are no longer available outside of FDA- and Institutional Review Board (IRB)-approved randomized controlled trials and may not be marketed or sold. FDA's appropriate caution in maintaining its usual criteria for licensure—of proving safety plus efficacy through two prospective randomly controlled trials (RCTs)—should not, however, misguide the physician about the potential future of amniotic products for the treatment of OA and tendinopathies or dissuade clinicians and researchers from continuing to investigate these useful products.

To date, both animal and human studies have shown that a single injection of amniotic suspension allograft

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(ASA) is safe, has not elicited any significant immune response, and has been shown to be effective in several prospective studies, and in at least one well-controlled randomized controlled human study for knee OA when compared to both hyaluronic acid and placebo saline.[1,2,3,4] The study in this issue, "A Single Injection of Amniotic Suspension Allograft Is Safe and Effective for Treatment of Mild to Moderate Hip Osteoarthritis: A Prospective Study" by Meadows, Elisman, Nho, Mowry, and Safron, has now expanded its use to suggest evidence of efficacy in mild to moderate hip OA, albeit in a small nonrandomized group.[5] This IRB-approved cohort study using good clinical practice guidelines once again supported the safety of this product and absence of any significant sequelae.

Amniotic tissue has a long history of use in both equine and human treatment of wound healing supporting its clinical effect on fighting chronic infection and inflammation.[6,7,8]

As an orthobiologic treatment, ASA and other amniotic products have several advantages. They save the patient from any invasive procedure for autologous harvest, decrease any potential side effects and discomfort for the patient, and allow the injecting physician to maintain an efficient practice in the office, while performing these injections. My own experience with these products has been very promising for the treatment of knee and hip OA. The question remains scientifically how might these work, as well as PRP, or other autologous products? Although a study from the Mayo clinic clearly showed that amnion and chorion have progenitor cells at the time of harvest, several studies have shown that after commercial preparation, few if any live cells remain in many of these products.[9,10] Therefore, it would seem, to quote Shakespeare, that something else is afoot. Studies by Kimmerling et al. using the same ASA suspension as used in the Meadows et al. article have shown that in rat OA models, injection increases IL-10 and induces monocytes to become M2 rather M1 macrophages, which both help to decrease inflammatory cytokine effects, decreasing proinflammatory cytokines and upregulating anti-inflammatory cytokines. [4] Furthermore, in non-OA models, Girolomo et al. have shown that ASA injected into Achilles tendinopathies of rats can improve fiber alignment and prevent evidence of degeneration,[11] Kimmerling et al. have shown that ASA can affect tenocytes, causing more robust migration, increased cell density, and decreased inflammatory markers, such as transforming growth factor β_1 compared to controls.[12] Luo et al. have shown effective use of a single intradiscal injection of ASA in a rat annular puncture model to treat intervertebral disc degeneration by looking at maintenance of disc height on a radiograph, T-2 signal of the disc on magnetic resonance imaging and histologic sections after death.[13]

In vitro studies from Flannery et al. on an alternate lyophilized amnion-chorion and umbilical cord product (PTP-001) have shown that this product can cause a dose-dependent decrease in tumor necrosis factor and IL-1β in an inflammatory model and also shows anticatabolic effect through a dose-dependent decrease in MMP 13, a matrix metalloproteinase that degrades collagen.[14] These basic science studies show that proteins in these harvested and processed tissues are anti-inflammatory, anticatabolic, and proanabolic and, therefore, seem to contain the "right stuff" to potentially treat chronic OA and tendinopathies in the future. An animal study in a rat OA model by the same authors showed this combined lyophilized amniotic product can prevent pain and cartilage degradation.[14]

Clinically, as discussed in the Meadows article, the ASA study groups of Gomoll et al. and Farr et al. have published both 6 and 12 month randomized controlled studies now over 2 years in 2 different journals, which show excellent results in the treatment of knee OA with a single injection with few complications.[1,2] Nunley et al. have published a prospective nonrandomized study on the use of a bioactive amniotic suspension product to achieve one- and two-level lumbar interbody fusions, again assuring safety and suggesting early efficacy.[15] Obviously, further randomized controlled large human trials of various joints are needed and should be encouraged, so that these products can be brought to market and made available to our patients safely and effectively.

I salute these authors along with all those moving forward with future studies and look forward to results, both from the basic science bench and human clinical RCT's, to help further elucidate the mechanism of action, and preferred dosing and targeting of these products for a variety of diseases. These IRB-approved, controlled studies are still the most well-recognized and effective way to advance the burgeoning field of regenerative orthopaedic products for our future armamentarium against these degenerative diseases that affect so many in our population and contribute to such significant disability. Postmarketing registries will then further enhance our real-world knowledge of these and other orthobiologic products and help define their responder profiles more accurately.

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