Amnion Injections: Evaluating a Brave New World of Regenerative Sports Medicine

This treatment offers a promising alternative for more rapid recovery.

BY ALBERTO ABREBAYA, DPM AND BEN PEARL, DPM

The cure for sports injuries is often elusive. Returning to sports without chronic pain or a permanent injury is most challenging for the professional athlete or the weekend-warrior. The expanding field of regenerative medicine now offers a new and promising treatment option in amniotic membrane injections. Recently published randomized studies and case articles report improvement with placental membrane injections. The literature supporting successful long-term outcomes of treatment with other regenerative treatments such as platelet-rich plasma (PRP) injections remains controversial. In contrast, amnion does not require the patient's own blood. Specifically, PRP and placental membrane both deliver a regenerative punch to the injured tissues by concentrating growth factors that recruit the body's own adult stem cells to repair the damage.

By regrowing the nascent cells, the injury can heal without the formation of dreaded scar tissue. Platelet-derived growth factors from PRP are monoclonal, therefore may be less effective in activating the damaged tissue cells to synthesize the interleukins, cytokines and prostaglandins necessary for the chemotaxis and adult stem-cell recoding. Recruitment of the subject's adult stem cells is hampered further by the significant differentiation of the adult mesenchymal stem cell, thus blocking the pathways to regrow into tissue progenitor cell lines. To improve these odds, leukocyte-rich supernatant can be extracted from the patient, but this requires a much larger volume (about a pint) of blood exfusion.

The placenta has been used for a century as a source of human donor tissue because of the regenerative properties provided by its natural biocompatibility, undifferentiated mesenchymal stem cells and lack of host rejection.[1] Mesenchymal stem/progenitor cells (MSCs) are present in the fetus (blood, liver, bone marrow, and kidney) and sparsely present in the adult human body (bone marrow, kidney, liver and lung). Research has shown that placenta-derived cells have multilineage osteogenic and adipogenic differentiation potential similar to MSCs in terms of morphology, cell-surface antigen expression, and gene expression patterns. The placenta is therefore a useful source of MSCs.[2]

Amnion cells are immune-privileged, lacking host vs. graft rejection. This immune naiveté is characteristic of the fetally-derived and maternal blood cells formed by the villous trophoblastic barrier. This contact between fetal foreign cells to the foreign immune system is the crucible for non-antigenic status of the placental cells with respect to antigens of the Major Histocompatibility Complex.

Properly processed placenta membrane preserves the complete spectrum of human growth factors. Cryopreserved living placental products deliver mesenchymal stem cells. Amnion injection stimulates a much more physiologic cascade of chemotaxis, inflammatory leukocyte infiltrate and remodeling by modulation of MSC in tissue colony aggregates that orchestrate ideal tissue healing and simulate the genesis of similar embryonic tissue cell lines in the fetus. These properties make placental an ideal treatment option for acute musculoskeletal injuries as well as chronic symptomatic conditions such as tendinosis and plantar fasciosis.

By regrowing the nascent cells, the injury can heal without the formation of dreaded scar tissue.

Tendons and ligaments are some of the strongest connective tissues of the body. They are subject to overuse injuries from cumulative microtrauma. Tendon cells (tenocytes) are elongated fibroblast-type cells. The cytoplasm is stretched between the collagen fibers of the tendon. They have a central cell nucleus. Tendon cells have a well-developed rough endoplasmic reticulum and

Continued on page 68

Getty Images/PhotoDisc

Amnion Injections *(from page 67)*

they are responsible for synthesis and turnover of tendon fibers and ground substance. Tendon cells form a connecting epithelial layer between the muscle.

Muscle cells are attached to the collagenous myotendinous space via hemidesmosomes. The TendoAchilles is subject to the highest strain of any tendon in the human body given the convergence of its form, function and corresponding anatomical musculature. It functions effecting plantarflexion of the foot with direct influence on forward propulsion and upward ejection and acceleration of the leg and lower segment of the thigh. The constant tension on the tendon exerts tremendous strain on the functional collagen microfibrular bundles at their insertion.

A limited vascular supply in this region is insufficient to provide ideal repair of the repetitive microtraumatic injuries to which the TendoAchilles is typically subjected. Age-dependent factors have also been documented in the demise of the TendoAchilles at the critical "watershed" or weakness zone.

Intrasubstance tears, tendinosis, and mucoid-myxoid degeneration are difficult to treat successfully without involving surgical methods. The current advancements in modern biotechnology have offered options to surgical repair with other minimally invasive techniques that have not provided quantifiable long term outcomes, such as extracorporeal shock wave therapy, radiofrequency-Coblation, etc.

Treatment Options

Treatment of sports injuries with amniotic membrane injection offers advantages over other invasive or surgical methods. Typically the patient will be evaluated with a thorough physical exam and different imaging modalities that may include radiographs, musculoskeletal ultrasound, MRI or a combination of these. Once the problem area is ascertained, standard treatment involves rest, ice, compression and elevation (RICE), custom orthoses, bracing, athletic strappings and physical therapy adjunctive modalities.

Amniotic injections offer a promising alternative for more rapid recovery. The product brand is selected by the physician's preferential experience. Several products are available in the market. Many are cryopreserved, some contain viable living cells, and others are combinations of dehydrated ultramicronized amnion-chorion membranes. Amniotic membrane products are also available with or without the chorion membrane. The addition of chorion is associated with a dose-dependent increased post injection temporary inflammatory flare-up.

As the use of these injections have increased with growing acceptance by the medical community, some manufacturers are releasing varying-dosed products targeted to the multiple specialties treating the different anatomical sites. Most (one is from umbilical cord) products are manufactured from donated placentas delivered from planned cesarean-section births and are processed under FDA-approved, proprietary-patented processes that consist of antisepsis with minimal tissue manipulation in order to qualify for human tissue implantation. All manufacturers are global US-based prestigious biotechnology companies with reputable track records.

Some companies are offering discount pricings for ordering Amnion units in bulk.

The office-based injection procedure involves provision of local anesthesia, preparation of the site with aseptic technique, reconstitution of the dry placental particulate or thawing of the prefilled cryopreserved syringe. The injection is then applied with minimal trauma to the patient and a light sterile bandage is applied. The practitioner may opt to immobilize the extremity for a short period using a CAM boot, recommend icing and narcotic analgesics for pain control if necessary.

The physician will also withhold post-injection corticosteroids and/or NSAIDs to avoid disrupting the prostaglandin and cytokine-mediated chemotaxis of pluripotential adult mesenchymal stem cells cascading to the treatment site activated by the injection of placental growth factors. The convalescence period is typically short, from 3–5 days of rest with gradual return to regular activity at the patient's own tolerance.

Costs vary by product manufacturer and range from $300 to $500 plus the physician's fee for the injection and manufacturer's charge for product shipping/handling. Some companies are offering discount pricings for ordering Amnion units in bulk. Amnion injections are not covered by insurance. It is debatable whether this trend may be reversing given the much lower relative cost of this office-based procedure versus the anesthesiologist's fee, cost of surgery, materials, and hospital operating suite.

Pat Agnew, DPM (Tidewater, VA) is involved in an ongoing randomized, single blinded multicenter trial with amnion injections for plantar fasciitis. These and other trials can be viewed at the NIH website: www.clinicaltrial.gov. He subscribes to his former residency director Jim Ganley, DPM's philosophy of how to succeed: don't fail. He would rather treat more patients at a lower cost for a therapy he feels is emerging. The authors have experience with tendon-injury injections with other amnion products, including favorable outcomes for a series of Achilles tendon injections by Dr. Alberto Abrebaya and Dr. Ben Pearl. Dr. Pearl injected his own Achilles tendon, which was instrumental in enabling him to get back to the soccer field. As long as no additional growth factors are added to the amnion injection, the therapy is permitted by USADA (United States Anti-Doping Agency). The injections are usually successful in a monotherapy regimen, which may be repeated as necessary in different anatomical areas without limitation, drug-interactions or dosage limitations until complete healing is achieved.

The authors refrain from prescribing post-injection non-steroidal anti-inflammatories (NSAIDs) to avoid disrupting the chemotaxis of pluripotential adult mesenchymal stem cells to the treatment site. In Dr. Abrebaya's practice, local injection of micronized human amnion-chorion membrane allograft has provided a powerful adjunctive therapeutic treatment for those patients afflicted with a broad range of chronic Tendoachilles, Tibialis Posterior, Peroneal tendinosis, plantar fasciitis/fascio-

Continued on page 70

Amnion Injections *(from page 68)*

sis and other joint symptomatic pathology. The injection involves the reconstitution of dHCAM micronized product in sterile water or sterile normosaline and injected into the visualized areas of TendoAchilles pathology.

To those patients for whom surgical intervention and the compulsory convalescence and rehabilitation regimens are not an option, the minimally invasive injection of micronized dHACM allograft has provided immense improvement and has become a viable non-surgical therapeutic treatment for Achilles tendinosis.

In conclusion, clinical experience is building a strong foundation of case-evidence for allograft injection of various amniotic membrane products. This alternative treatment can further enhance non-surgical healing of sports injuries from Achilles tendinosis, tibialis and peroneal tendinopathies, plantar fasciitis and other connective tissue bone and joint disorders. Further study of the mechanism of action of amniotic membrane on the physiology of tendon healing will inevitably unveil useful information enhancing the successful outcomes for these types of regenerative therapies in many debilitating musculoskeletal ailments, which currently embody the "Achilles Heel" of non-surgical treatments for sports injuries. **PM**

References

[1] Human Placenta-Derived Cells Have Mesenchymal Stem/Progenitor Cell Potential Yumi Fukuchi Ph.D.*, Hideaki

[2] Nakajima, Daisuke Sugiyama, Imiko Hirose, Toshio Kitamura and Kohichiro Tsuji

[3] Article first published online: 1 SEP 2004 DOI: 10.1634/stemcells.22-5-649

[4] HLA Class I protein expression in the human placenta. Blaschitz A1, Hutter H, Dohr G.

[5] Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors Kazutoshi Takahashi[1], Shinya Yamanaka[1,2]

[6] Zelen, Charles M., Poka, A., Andrews, J., Prospective, Randomized, Blinded, Comparative Study of Injectable Micronized Dehydrated Amniotic/Chorionic Membrane Allograft for Plantar Fasciitis—a Feasibility Study. Foot Ankle Int. August 2013; 34: 1332.

Dr. Alberto Abrebaya is a private practitioner in Miami, Florida, serves as affiliate faculty to Barry University School of Podiatric Medicine, is a staff-podiatrist at West Palm Beach VA Medical center, and is a Diplomate of the American Board of Foot and Ankle Surgeons and a Fellow of the American Professional Wound Care Association. Additionally, Dr. Abrebaya is an active member of the NIH-affiliated Minority Research Program at Florida International University.

Dr. Ben Pearl is a private practitioner in Arlington, Virginia, and serves as a consultant at the National Institutes of Health and is a Fellow of the American Academy of Podiatric Sports Medicine.