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Regenerative Medicine for Tendinous and Ligamentous Injuries of Sport Horses

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After tendon injury, the scar tissue that replaces the damaged tendon results in reduced performance and a substantial risk for reinjury; there is a 56% risk for reinjury for National Hunt jump horses, and 66% of flat-track race horses had reinjury after superficial digital flexor tendon (SDFT) tendinopathy [1]. Therefore, if these poor functional outcomes are going to be avoided, it is necessary to replace the injured tissue with a matrix more like tendon and less like scar tissue. The goal of regenerative therapies is to restore normal structural architecture and biomechanical function to an injured tissue. Successful restoration processes for any tissue are thought to recapitulate those of development, in which there are spatial and temporal interactions between scaffold, growth factors, and cell populations [2]. An understanding of the molecular and mechanical processes involved in the development of tendon versus ligamentous injuries and between acute and repetitive overload pathologic conditions can help to guide development of target therapies for each specific disorder. Regardless of the inciting cause, regeneration of complex tissue structures, such as tendon and ligament, is likely to require therapies that contain these three components: scaffold, growth factor(s), and cells.

For many of the therapeutics presently available, technology and marketing are ahead of laboratory or clinical research; therefore, most of the

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products that are commonly used have not been fully evaluated for safety or efficacy in tendons or ligaments. Although some short-term safety trials have been performed, stem cell–treated cases have now been followed for up to 5 years without evidence of adverse effects, such as tumor growth. Ideally, the efficacy of products should be evaluated based on the outcome of prospective, blind, and controlled clinical trials, although, practically, these are exceedingly difficult to execute in performance horse populations. At a minimum, results should be compared with carefully selected historical case-matched controls that reflect the treated cases for retrospective analyses. Regardless of the modality chosen to attempt tendon or ligament regeneration, a commonality in all treatments includes serial ultrasonographic monitoring of linear and cross-sectional fiber pattern and a graded increasing exercise program.

Scaffold-based therapies

Urinary bladder matrix (UBM; a product of ACell Inc., Columbia, Maryland) scaffolds are derived from the urinary bladder of pigs. Mechanical and chemical processing is used to isolate the basement membrane and tunica propria layers, which are further processed into sheets or powder. Application of UBM is thought to provide an inductive scaffold for tissue replacement by the host and to stimulate neovascularization in the site of injury, although this has not been investigated or proved. For injection into tendons or ligaments, UBM powder is reconstituted in saline (0.03–0.04 g/mL) and injected under ultrasonographic guidance into the lesion. When the product is purchased, the company provides details on application and postinjection protocols. To minimize postinjection swelling, the injected limb is iced and flunixin meglumine is administered to horses. Additional critical factors that are believed to be related to postinjection swelling including ''overfilling'' of defects based on ultrasonographic appearance and injection during the acute inflammatory phase at 7 to 10 days after injury. Presently, there are no specified differences in treatment protocol for tendon as compared with ligament treatment with UBM. In the United States, several hundred horses (primarily sport horses) with tendonitis and suspensory ligament desmitis have been treated with UBM. Preliminary reports suggest that UBM treatment is successful in returning approximately 85% of horses to soundness at the original level of performance [3]. This outcome measure has some relevance to suspensory ligament desmitis; however, because long-term lameness is not a feature of superficial digital flexor tendonitis, this does not provide a reliable outcome measure for this disease.

Growth factor–enhanced regeneration

Many medical treatments for equine tendonitis/desmitis have centered on delivery of a single or multiple growth factors to the site of injury. Growth

factors are protein-signaling molecules that regulate cellular metabolism. They enhance tendon and ligament healing by stimulating cell proliferation, increasing extracellular matrix synthesis, and promoting vascular ingrowth. In addition to their anabolic effects, growth factors downregulate catabolic matrix-degrading cytokines, such as interleukins and matrix metalloproteinases [4–9].

The growth factors most widely studied in tendon and ligament healing include insulin-like growth factor-I (IGF-I), platelet-derived growth factor (PDGF), bone morphogenetic protein-12 (BMP-12), transforming growth factor-β (TGFβ), vascular endothelial growth factor (VEGF), growth/differentiation factor (GDF-5), and basic fibroblast growth factor (bFGF) [4–9]. Growth factors are available as recombinant purified proteins or within a less defined slurry of bone marrow (BM) aspirate or platelet-rich plasma (PRP). Clinical delivery of growth factor(s) to a tendon or ligament is by means of a series of intralesional injections; gene therapy techniques to deliver more sustained levels of IGF-I are being investigated in equine models of SDFT tendonitis [10]. There are a plethora of in vitro and in vivo animal studies demonstrating the advantages of using growth factors for enhanced healing of tendonitis/desmitis and tendon lacerations; however, despite the numerous experimental studies, there is little long-term multicenter human or equine data on clinical cases available for any of the growth factors.

Transforming growth factor-β

The results of a prospective 3-year study examining the efficacy of TGF-β1 to augment healing of equine SDFT tendonitis (10 cases) and suspensory desmitis (1 case) have been reported [11]. In that study, all horses returned to their previous level of athletic use, but 40% injured the contralateral untreated SDFT and 60% of horses had palpably enlarged tendons in the treatment area. Because of the contralateral limb injury rate, TGFβ is no longer used clinically, although the treatment of both limbs, which would be in keeping with our knowledge that many, if not all, of these strain injuries have bilateral components, may improve the outcome.

Insulin-like growth factor-I

Intralesional administration of IGF-I has been reported to enhance return of tendon fiber pattern and improve mechanical characteristics in a collagenase-induced SDFT tendonitis model [8,12]. In clinical cases of SDFT tendonitis in thoroughbred race horses, IGF-I administration is preferably performed in horses that also receive tenoscopic bilateral transection of the accessory ligament of the SDFT to minimize recurrence of tendonitis [13]. Not all horses that received IGF-I injections were also operated on because of financial constraints. The injection protocol consists of IGF-I

(human recombinant IGF-I) at a dose of 25 to 50 μg injected into the lesion using ultrasound guidance on days 1, 4, 7, and 10, with surgery being performed on day 2 or 3. A retrospective study of 39 thoroughbred race horses (treated with IGF-I and desmotomy) with a follow-up duration of more than 12 months reveals that 9 (23%) have raced more than five times without further tendon or ligament injury. Of 28 horses for which the ultimate outcome is known, 13 (33%) rebowed the injected limb and 7 were retired for injuries to musculoskeletal tissues other than tendon. One horse had suspensory desmitis on the treated limb, and 2 were retired to breeding without further work [13]. These results are comparable to those previously reported for flat-track racehorses treated with conservative therapy only or with intralesional injections of β-aminopropionitrile (BAPTN), polysulfated glycosaminoglycan, or hyaluronan [1].

Platelet-rich plasma

PRP is blood plasma with a concentrated platelet count, generally greater than two to four times normal. PRP is generated through a simple centrifugation or filtration process of venous blood to concentrate the platelets. The role of platelets in homeostasis is well known. PRP is an attractive biologic tool to enhance tendon and ligament regeneration, however, because platelets are also a natural reservoir of a pool of growth factors, including PDGF, TGFβ, and VEGF, all of which have been shown in vitro and in in vivo animal models to enhance tendon regeneration [4–9]. Platelet degranulation is thought to release the growth factors and other substances that promote tissue repair and influence the reactivity of vascular and other blood cells in angiogenesis and inflammation. The advantages of using PRP include ease of use, administration of autologous peptides, and delivery of a combination of growth factors. In addition, PRP clots after injection through exposure of platelet to the basement membrane of cells in damaged tissue, resulting in the formation of a fibrin scaffold to allow for cellular migration into the injury and as a mechanism to retain the growth factors at the site of injury. The primary disadvantage of PRP is that it lacks a cell source and delivers a mix of growth factors associated naturally with scar healing. In an explant culture system, however, tendons cultured in pure PRP showed enhanced gene expression of those matrix molecules characteristic of tendon, including cartilage oligomeric matrix protein (COMP) and an increased collagen type I/collagen type III ratio, with no concomitant increase in the catabolic molecule matrix metalloproteinase 3 or 13 [14]. Suspensory ligament fibroblast matrix production is also stimulated by addition of PRP but to a lesser extent than by application of BM supernatant [15,16]. These findings support the in vivo investigation of PRP as an autogenous patient-side treatment for tendonitis and suspensory desmitis. In the clinical arena, horses are presently being treated with PRP; however, long-term follow-up is not yet available.

Stem cell therapies

Although growth factors seem to enhance tendon and ligament regeneration and repair, efforts to improve healing further are currently centered on the delivery of stem cells to the site of injury. In horses, the greatest clinical interests are in the application of adipose- and BM-derived stem cells for tendon healing, and variations of both cell types are being used clinically with reported success. Arguments can be made for a stem cell source being optimal for applications in regenerative therapies, and, importantly, studies are needed to define the necessity of stem cells in such endeavors. There are more data available regarding cartilage tissue engineering, and those data support the need for the presence of cells (chondrocytes or stem cells) in a graft composite, but similar data are less abundant for tendon regenerative studies [17–19].

Mesenchymal stem cells from bone marrow aspirate

The use of BM-derived mesenchymal stem cells (MSCs) is supported by experimental studies in laboratory animals of MSC implantation in surgical lesions, which have shown favorable effects on tissue organization, composition, and mechanics of MSC-implanted tendons and ligaments over controls [20,21].

There are currently three techniques available for the treatment of tendon and ligament injuries with BM-derived MSCs. One uses direct injection of the heterogeneous mixed-cell population in a BM aspirate; another uses centrifugation, similar to that used to generate PRP, with the aim of increasing the number of stem cells in each injection; and the third relies on a cultured cell population derived from BM. Each technique has its strengths and weaknesses.

In the first technique, BM aspirate is collected from the sternum (or the tuber coxae) under sedation and local anesthesia (Fig. 1). The site(s) for BM injection is approximately where the center of a girth would be located on the sternum. Ultrasonography is used by some to locate the sternebrae to avoid inadvertent penetration of the intersternebral space, which could lead to negative aspiration, or introduction of the needle caudal to the sternum, which could lead to puncture of the heart. Bone penetration and aspiration are facilitated by use of a BM (Jamshidi) biopsy needle with a double-diamond stylet and interlocking T-handle (Fig. 2), with an inner-diameter cannula (eg, 11 gauge $\times$ 100 mm). Ideally, the site of injection in the tendon is aseptically prepared for injection before performing the BM aspiration so that the BM can be injected immediately after isolation to avoid clotting. If performed efficiently, anticoagulant is not necessary, which further simplifies the direct aspiration-injection approach. Advantages of this procedure are the simplicity of the technique, ability to perform the procedure immediately at the time of diagnosis, and relatively low cost. There is some concern over the use of BM aspirate in tendons because of the potential for mineralization, but the incidence of such an event seems

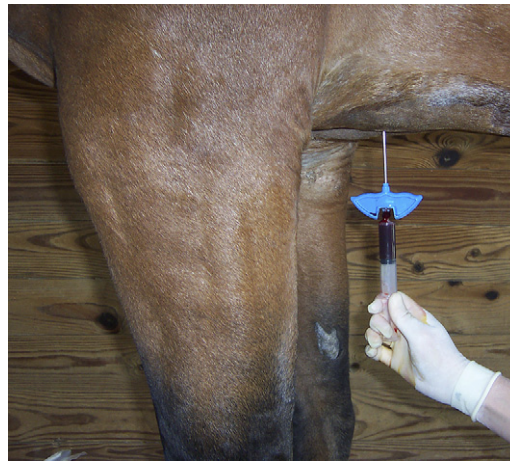

Fig. 1. Site for BM aspiration from the sternum is approximately where the center of a girth would be located.

to be low. The primary disadvantage is the small number of stem cells that are contained in raw BM aspirates. In human beings and cats, the number of stem cells in raw BM is reportedly 0.001% to 0.01% of the mononuclear cell population [22,23].

The second type of procedure using BM-derived MSCs can also be used at the time of diagnosis and is generally targeted toward increasing the concentration of MSCs for direct injection. In this procedure, 60 mL of BM aspirate is collected into syringes containing heparin (1 mL of 500 U/mL heparin) to prevent coagulation. The BM aspirate is then subjected to centrifugation in a HarvestTechII (Harvest Technologies, Plymouth, Massachusetts) machine for 14 minutes to concentrate mononuclear cell

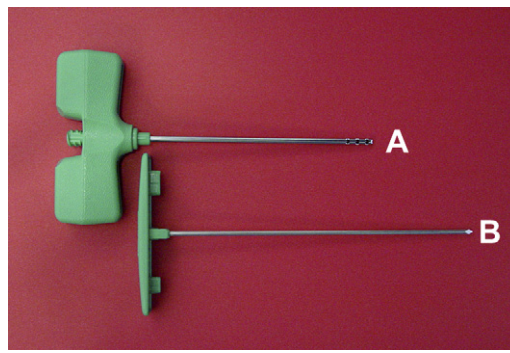

Fig. 2. Jamshidi BM biopsy needle with interlocking handle (*A*) and a double-diamond point stylet (*B*) are shown.

populations, including MSCs [24]. Using a range of six to eight cell surface markers, this procedure seems to generate a 12-fold concentrate of putative MSCs [24]. BM aspirate concentrate has all the advantages of PRP and BM aspirates, including their autogenous nature and ability to be performed at the time of diagnosis, and it contains all three components for optimal tendon and ligament regeneration: scaffold, growth factors [14,15], and stem cells. BM aspirate concentrate is presently being evaluated in vitro and in vivo to determine its effects on suspensory ligament regeneration.

Finally, BM-derived MSCs can be used after expansion of the nucleated adherent cell population (containing the MSCs) in the laboratory. A 2- to 3-week culture period is then needed to expand the selected cells until more than 10×10^6 cells are available for implantation under standing sedation into the tendon core lesion using ultrasound guidance. The cells are suspended in BM supernatant for implantation so that no "foreign" material is implanted and to gain potential beneficial effects of the rich growth factors present in the supernatant [14,15]. The advantages of this technique are that a more "pure" and possibly greater number of stem cells are implanted, but the disadvantages are the delay between BM aspiration and implantation and the increased cost.

More than 500 horses have been treated with this technique. At the most recent evaluation of clinical outcome (September 2006; Table 1), 168 racehorses had been treated and long-term (>1 year) follow-up was available for 82 horses. For National Hunt racehorses (n = 71), the reinjury rate was 13% (including injuries to untreated contralateral limbs). When only those horses that had entered full training were included, the reinjury rate rose slightly to 18%. This compares favorably with previous analyses for the same category of horse (56% reinjury rate for National Hunt horses reported by Dyson [1]), although this analysis was more than 2 years rather

Table 1
Reinjury rates after BM-MSC treatment

Use	No. SDFTs treated	SDFT treatment with follow-up for >1 year	Success rate (no reinjury): those horses returned to full training for >1 year in full work, both limbs	Success rate (no reinjury): conventional treatment, those horses returned to full training for >2 years in full work, both limbs [1]
National Hunt	145	71	82%	44%
Flat	23	11	50%	34%
Total (all racehorses)	168	82	78%	43%

than 1 year after a return to full work. Further follow-up of these treated horses after this period should allow direct comparison. In further support for this improvement in outcome, however, reinjury rates for sports horses (all disciplines combined; n = 24 with more than 1 year of follow-up) was improved by a similar degree (13% compared with 23%–43% reported for different sports horse disciplines by Dyson [1]).

When comparing those horses that did not reinjure themselves with those that did, there was a significantly longer interval between injury and implantation for the failures (83 days versus 44 days; $P = .0035$). It is hypothesized that this was attributable to the later implanted horses having substantial fibrosis present within the healing tendon before implantation, which may have compromised the efficacy of the treatment. Earlier aspiration of BM, and hence implantation, is now recommended in an attempt to avoid this. The aim is to implant after the inflammatory phase but before fibrous tissue formation (practically, this means aspirating the BM ideally within 1 month of injury). The time of implantation may be further optimized by preinjury storage of cells or the use of umbilical cord cells recovered at the time of birth and stored for future use.

The MSC applications described thus far use autogenous cells. The use of allogenic grafts would avoid the culture interval; however, as yet, we do not have the necessary tools to select the optimal cell line, and there are also regulatory issues to be overcome. In laboratory animals and human beings, there was early evidence that MSCs were immunoprivileged; therefore, allogeneic grafts could be used [25]. More recently, it has been shown that MSCs induce memory T-cell and natural killer T-cell responses in immune-competent hosts [25]. Therefore, until further investigations are performed, allogeneic graft should not be used.

Adipose-derived mesenchymal stem cells

This technique is based on data suggesting that adipose-derived MSCs (A-MSCs) exhibited a similar degree of multipotentiality to BM-MSCs, although in many studies, they perform less well than BM-MSCs in differentiation assays [26,27]. The currently available technique uses a mixture of cells derived from the adipose tissue (taken surgically from the tail head) once the cells containing fat have been removed; there is no culture step. This has the advantage of supplying large numbers of cells (but with an undetermined number being MSCs) in a short period (48 hours). The cells are implanted under ultrasound guidance as outlined previously. No references regarding the clinical application of A-MSCs in equine tendonitis are presently available, although the results of a pilot study with two groups of four horses in which lesions were created in the SDFT with collagenase demonstrated significant improvement in histologic score in the A-MSC–treated tendons over phosphate-buffered saline–treated control tendons [28].

Surgical manipulations: adjunctives to therapies for tendon and ligament regeneration

Tenoscopic desmotomy of the accessory ligament of the SDFT (proximal check ligament) should be considered for animals with SDFT lesions [29]. Transection of the check ligament lengthens the musculotendinous unit, which should help to compensate for the loss of elasticity associated with tendon scar formation, thereby diminishing the incidence of rebowing and relocating the point of maximal strain within the tendon. Some but not all studies have suggested an increased incidence of suspensory desmitis after proximal check ligament desmotomy [30,31], which, although being supportive of the hypothesis behind this procedure, is not a concern in the authors'; experiences.

In such areas as the fetlock canal, carpal canal, and proximal suspensory ligament region and where tendon and ligament are anatomically confined by surrounding structures, and thus could be compressed, surgical release of the restricting fascia has been suggested. Compression of tendons and ligaments and associated neurovascular structures is typically attributable to chronic enlargement of the tendon or ligament within a confined space and not to actual enlargement of the surrounding fascial structures impinging on a tendon or ligament of normal anatomic dimensions. The regions most commonly affected are the deep digital flexor tendon within the fetlock canal, the musculotendinous junction of the SDFT within the carpal canal, and the origin of the suspensory ligament within the surrounding fascia. Release of the surrounding fascial structures is thought to enhance neurovascular supply and decrease abnormal mechanical compression to the affected region, thereby enhancing regeneration and diminishing vasogenic or neurogenic pain. The surgical techniques for tenoscopic carpal canal release [32], metacarpophalangeal/metatarsophalangeal annular ligament transection [33], and fasciotomy of the proximal suspensory ligament have been reported [34]. These surgical techniques should be considered as one part of a multitargeted approach to tendon and ligament regeneration, with careful attention also applied to medical therapy and a controlled rehabilitation exercise program.

Ultimately, side-by-side evaluation of the various biologic products presently available for tendon and ligament regeneration needs to be performed to provide an indication of the most appropriate treatment for tendon or ligamentous injury. In addition, an improved understanding of tendon and ligament development should guide development of future regenerative therapies aimed at recapitulating the development process during restoration of normal tendon and ligament molecular and mechanical properties.

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