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Case Report

Ortho-Biologic Treatment of Partial Thickness Rotator Cuff Tears with T2 Wetmap MRI Follow Up

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Abstract

Treatment of partial thickness tears of the rotator cuff is controversial in orthopedic surgery and the optimum treatment strategies continue to evolve. Recommendations vary widely across the spectrum from benign neglect with physical therapy, to surgical *in-situ* repair or takedown of the partial thickness tear to create a complete tear, followed by arthroscopic or open reconstruction.

In 2006, we developed an experimental, autologous orthobiologic treatment for partial thickness tears of the rotator cuff with the goal of restoration of tissue biology and function using autologous bone marrow nucleated cell concentrate suspended in a fibrin matrix growth factor concentrate. The technique includes autologous bone marrow injectate modification within the legal limits of human tissue and cell product transplantation. The technique also includes low intensity pulsed ultrasound and tailored physical therapy depending on tear size, morphology and patient specific issues.

This report details the treatment technique and posits mechanisms of treatment action responsible for the clinical success of treatment and includes a case presentation for discussion.

Keywords: *Mesenchymal Stem Cells (MSC); Stem Cells; Orthopedic Biologics; Low Intensity Pulsed Ultrasound (LIPUS); Partial Thickness Rotator Cuff Tears; Degenerative Rotator Cuff Tears*

Introduction

Partial thickness rotator cuffs are a common cause of shoulder pain and disability and are typically classified by location, depth and tear area [1,2]. Currently, management of partial thickness tears of the rotator cuff (PTRCT) is controversial at least in part because PTRCTs do not represent a single entity, but rather a clinical spectrum of disease [3]. Partial thickness tears of the rotator cuff have the potential to cause significant clinical misery and functional limitations and have been linked to degenerative microvascular abnormalities that could be amenable to biologic stimulation [4]. Partial thickness tears can be on the articular or bursal side of the tendon [5]. There is wide variability in size, location, etiology and biologic condition of the tendon and tissues surrounding the glenohumeral articulation, complicating clinical decision making [6]. Degenerative rotator cuff tears are the most common cause of shoulder pain and have a strong association with advanced aging [7]. Factors potentially influencing the rate of successful tendon healing include age, tear size and severity of muscle degenerative changes in addition to general health fitness and local tissue factors [8]. Local tissue factors are significant and may be primarily responsible for the clinical failures of treatment [9]. Based on cadveric and imaging studies, the prevalence of PTRCTs

ranges from 13%-32% with a strong correlation to patient age [10]. In overhead athletes, the overall prevalence has been reported as high as 40% [11].

Reduced vascular penetration to the watershed footprint of the rotator cuff, coupled with reduced tensile strength of the tendon on the articular side as opposed to the bursal side lead to partial thickness tears of the articular side in a degenerative pattern [12]. Partial thickness tears of the rotator cuff in younger patients represents a different subset of lesions and typically tears are seen more posteriorly and at the rotator interval [13]. In the presence of a partial thickness rotator cuff tear, strain patterns of the remaining intact cuff are impacted [14]. In addition, there is limited intrinsic ability of the tendon to spontaneously heal due to biologic factors that the described treatment addresses primarily at the nanoplastic cellular level through immunomodulatory cell signaling pathways that may function through cell hysteresis to regenerative and anti-inflammatory pathways [15,16].

From 2006-2009, we developed an experimental, autologous orthobiologic treatment for partial thickness tears of the rotator cuff with the goal of restoration of tissue biology and function using autologous bone marrow nucleated cell concentrate suspended in a fibrin matrix growth factor concentrate. The technique includes autologous bone marrow injectate modification within the legal limits of human tissue product transplantation [17]. The technique also includes low intensity pulsed ultrasound and tailored physical therapy depending on tear size, morphology and patient specific issues [18].

Conservative treatment

Conservative treatment of patients with partial thickness rotator cuffs that restores shoulder range of motion, in particular internal rotation, is frequently effective in reducing pain and improving function [19]. Traditionally, failure of multimodality conservative measures may indicate surgical intervention. A variety of different approaches to address partial thickness rotator cuff tears have been delineated throughout the literature with varying results regardless of the treatment modality suggested [20]. Prolonged exercise rehabilitation has been recommended as the initial treatment of all partial thickness rotator cuff tears because patients opting for physical therapy have demonstrated high satisfaction, an improvement in function and success in avoiding surgery [21]. The development of a minimally invasive, biologic approach to management could avoid a great deal of patient morbidity and dissatisfaction with currently available treatment means. Unlike full thickness tears, the risk of fatty infiltration, muscular atrophy and tear extension requiring surgery are relatively minimal [22].

Surgical treatment

A failure of non-surgical treatment for six months generally indicates surgical treatment. The major surgical decision that must be made is what type of operative intervention is most likely to benefit the patient. Superior results have been reported for PTRCT repair when tear thickness exceeds 50% versus debridement [23]. Biomechanical studies have found an increase in rotator cuff strain between intact tendons and PTRCTs involving > 50% of the tendon thickness [24]. Patients exhibiting considerable weakness and functional disability may benefit from repair even in the setting of smaller rotator cuff tears [25].

Surgical treatment of PTRCTs is not uniform and includes techniques ranging from arthroscopic debridement to *in-situ* repair to completion of the tear with open reconstruction [26-31]. Some authors have concluded that *in-situ* transtendinous repair outperforms tear completion and repair for partial articular sided supraspinatus tendon tears [32]. Further research is required to determine the clinical indications for surgical management and which treatment methods are most likely to result in successful results. Many surgical techniques have been described, yet there is no clinical research available to support more complex surgical repairs over standard rotator cuff repair. With the advent of biologic adjunctive therapies over the last decade, more questions than answers have surfaced, prompting additional research at the basic science and clinical level.

Surgical treatment of PTRCTs may result in stiffness, decreased range of motion and strength losses in the short term which has led some authors to question whether athletic populations are at higher risk for complications with surgical repair [33]. Similarly, some

authors have recommended debridement with acromioplasty over *in-situ* repair or completion of PTRCTs with repair in the setting of an overhead athlete with partial thickness rotator cuff pathology.

Orthobiologic treatment

Orthopedic surgical biologic treatments are not new. We incorporated concentrated autologous bone marrow products into our surgical rotator cuff repair procedures beginning in 2006. Excellent results in that patient population even where massive tears of the rotator cuff requiring reversed dermal allograft tissue were encountered led us to consider the viability of orthobiologic treatment in the setting of partial thickness rotator cuff tears. Other authors have focused on biologically augmenting reconstruction of the rotator cuff to improve tendon-bone healing [34]. Varying measures with products including heterogenous platelet concentrates, mesenchymal stem cells and a combination of products have been reported [34]. Interest has been piqued with some reports of 94% failed healing in patients undergoing rotator cuff repair without biologic augmentation [35]. The high rates of failure are attributed to intrinsic degenerative changes in the tendon, rather low cellularity and the poor vascular supply to the cuff footprint. The inflammatory healing process depends on the ability of environmental proteins to favor an anabolic condition in the tissues. Biologic augmentation of tissues provides vital proteins known as cytokines that enhance immunomodulatory signaling resulting in an anti-inflammatory environment that is conducive to tissue repair and regeneration. Through orthobiologic modification, destructive catabolic pathways are reversed. Growth factors are only a part of the equation and come from lysis of platelet dense granules that is part of the directed procedure. Several authors have reported on the experimental value of BMP, TGF and FGF in the setting of rotator cuff tear noting an increased load-to-failure and an increased bone and soft tissue volume where biologic augmentation was used [36-38].

Catabolic pathways typically involve elaboration of monocyte-derived pro-inflammatory cytokines that drive the degenerative process and include IL-1, TNF-alpha, IL-1, IL-6, IL-8, IL-17, IL-18, LIF, OSM and most prostaglandins. The small molecular size of these molecules makes nanofiltration and elimination possible (30 kD) where filter pores are typically 55 - 65 kD. Conversely, anti-inflammatory molecules, excluding TSG-6, are large and easily sequestered in a growth factor concentrate that is used in a fibrin scaffold that has been thrombinated to ensure it stays where directed. Anti-inflammatory molecules of interest in this setting include sTNFr, IL-4, IL-10, IL-11, IL-1 receptor antagonist protein (IRAP), Alpha-2-macroglobulin and TSG-6. Due to its small molecular size (~30 kD) unless specific steps are taken to activate and concentrate TSG-6, it is lost in the nanofiltration step and may represent the most important component of the treatment given its unique designation as a "chondroprotective' molecule.

Cell based augmentation has emerged as the most advanced strategy in rotator cuff biologic management. While considerable attention has been focused on the adult mesenchymal stem cell that resides in all tissues and can replaced different dying cells in a tissue, it is more likely a combination of all nucleated cells from a bone marrow concentrate that contribute to the favorable immunomodulatory signaling. Several experimental protocols have been suggested to accomplish this end. One study of rotator cuff tears augmented with bone marrow concentrate demonstrated good tendon integrity in all subjects on MRI [39]. Several authors have concluded that there is great need for biological augmentation of rotator cuff tears as a result of the high published re-tear rate. Using cells to biologically augment partial thickness rotator cuff tears through a minimally invasive approach would be a desirable approach given it's minimal morbidity and ability to enhance the healing milieu of the cuff tendons [40]. We believe that biologics in the setting of PTRCTs may represent an ideal approach or part of a staged approach to management of these common lesions.

Case Report

The patient is a 65-year-old elite level golf athlete who presented in December 2018 with complaints of right shoulder pain that had increased in intensity and failed multimodality conservative treatments including activity modification, physical therapy and OTC remedies including cannabidiol products.

The patient complained of right shoulder pain with nighttime exacerbation and limited mobility of the right shoulder with activity. The patient reported increasing difficulty with his desired recreational and vocational pursuits due to the right shoulder pain.

Physical examination

Examination at the time of presentation revealed a fit, 65-year-old male complaining of anterolateral right shoulder pain without radiation.

The cervical spine examination was normal.

There was no periscapular atrophy or shoulder girdle dysmorphology. Motor was graded as 5/5 and equal in forward elevation, external rotation and internal rotation. There was point tenderness to palpation of the supraspinatus and rotator interval on examination. There was no scapular dysmotility.

Range of motion of the affected right side initially demonstrated posterior capsular contracture with a difference of six vertebral levels. The patient's internal rotation was to T9 on the unaffected left side and L3 on the right. In addition, there was slight limitation in forward elevation (170º versus 160º), external rotation in adduction (55º versus 70º) and external rotation at 90º (80º versus 90º).

No instability was detected in any plane. Apprehension, relocation and load-shift tests were negative with a negative sulcus sign. Neer and Hawkins tests were equivocal. Speed's and Yergason's tests were negative. Physical therapy with manual stretching was indicated to restore range of motion prior to considering the patient for candidacy for the procedure.

Radiographs

Initial radiographic studies of the patient's right shoulder included scapular AP, Grashey view, scapular-y lateral and axillary views. These images demonstrated severe AC arthrosis and mild arthrosis of the glenohumeral articulation that was confirmed on MR sequencing.

Magnetic Resonance Cartigram® Sequencing (General Electric, Chicago, Illinois) was performed in the injury setting and post operatively at follow up. The patient's initial MR revealed a linear partial tear of the articular side of the rotator cuff with an intrasubstance component extending to the supraspinatus and tendinosis of the supraspinatus. A type 1 SLAP tear was noted. Mild degenerative disease of the glenohumeral articulation was present (Figure 1).

Orthobiologic treatment

The patient was seen and evaluated. Once a thorough history and physical examination had been accomplished, physical therapy with manual stretching was recommended for capsular stretching. The patient was advised that he would not be a candidate for the procedure until he was able to demonstrate a full range of motion, including internal rotation (T9) that matched the contralateral, unaffected side. At the time of the procedure, the patient had a range of motion and motor examination that matched the unaffected contralateral limb and required six weeks of a physical therapy program to achieve that end. In spite of improvement with physical therapy, the patient's persistent pain precluded his ability to enjoy desired recreational and vocational pursuits.

Informed consent was obtained with a deliberate focus on educating the patient that the shoulder 'Nanoplasty™' was an experimental treatment being used 'off-label'. While the procedure and devices are 'FDA-cleared', they are not 'FDA-approved' for the indication.

The procedure is performed in an office procedure room with laminar flow and under meticulous sterile conditions. The patient is initially positioned supine for iliac crest bone marrow aspiration coincident with the anterior gluteal pillar which can easily be palpated as the thickened genu of the anterolateral pelvis four finger breadths (7.0 cm) posterior to the anterior superior iliac spine (ASIS). Bone marrow harvest is by Jamshidi needle tip approximately 3 cm deep with care taken to rotate the needle and maximize nucleated cell count. Thrombin harvest is accomplished with a final dedicated syringe of the marrow aspirate using the Arthrex® Thrombinator®. The bone marrow aspirate is concentrated with isopycnic separation to achieve a layer of nucleated cells where mesenchymal bone marrow

cells reside (0.01% of marrow cells). The plasma layer is activated for TSG-6 with hyaluronic acid prior to passage through a with 65 kiloDaltons (kD) nanopores that excludes pro-inflammatory molecules and water. In general, pro-inflammatory mediators are ~30 kD in size. The growth factor concentrate then serves as an activated cellular scaffold to which autologous thrombin is added to stabilize the transplanted cells. Once the gel injectate has been placed onto the Mayo stand, the injection component of the procedure commences under a new sterile field.

Both static and dynamic ultrasound are used to visualize the lesion which is compared to MR Cartigram® images obtained in the pre-operative setting. The patient is placed into the beach chair position with easy access to the shoulder. The 'hand-on-hip- position puts the supraspinatus tendon in line with needle advancement which is in line with the fibers of the tendon. The tendon defect is identified easily with ultrasound (Phillips® Lumify®) and indirect visualization of an 18 ga spinal needle tip is accomplished, allowing for the optimal trajectory starting approximately 2 fingerbreadths below the lateral acromion. Injection is accomplished from a medial to lateral direction with withdrawal of the needle and visualization of the injectate leaving the needle into the substance of the tendon. Once the lesion has been crossed and injected line with the tendinous fibers and depending on the tear location, a 22 ga spinal needle is then used to cross the initial injection tracts at a right angle from anterior to posterior, forming a crosshatched configuration. Finally, the Jamshidi is driven into the base of the tear at the tendinous insertion where aspiration of 5 mL of marrow from the humeral head is accomplished. The final aliquot of bone marrow concentrate is injected into the bony rotator cuff footprint coincident with the specific tear being addressed [41,42].

The procedure is well-tolerated, and patients are ambulatory to home within thirty minutes of completion. Patient post-operative protocols are specifically tailored to the individual and depends on tear characteristics and clinical performance goals post treatment with fine tuning required during the first six weeks following the injection. In general, patients are out of an Ossur® Smartsling II® with an abductor pillow immediately for range of motion but wear the sling for approximately six weeks to allow for tissue healing. By six weeks the patient should have maintained their pre-operative range of motion and usually begins strengthening. By twelve weeks patients are typically pain free and begin activity specific PT and by six months all of our patients have returned to recreational and vocational pursuits without limitation.

Follow up MR Cartigrams are obtained at one and two years to evaluate anatomic healing of the tendon lesion and we have been pleased by the results (Figure 1 and 2) demonstrates pre and post procedure changes in the tendon. Enhanced proteoglycan signaling consistent with novel tissue growth by virtue of hydration signal can be noted at the tear interval. The Cartigram® delineates the previously noted delamination tear has been healed during the imaging interval and can be seen in the figures.

Orthobiologics mechanisms of action

Signaling cells

Stem cell concentrates are more appropriately referred to as signaling cell concentrates. The term 'stem cell' has been abused in the open market to infer to patients that they would be receiving a direct medical benefit because they imagine the cells will differentiate into regenerating tissue-producing cells. In fact, these cells home in on sites of injury and disease and secrete bioactive factors that are immunomodulatory and regenerative. It is the patient's own site-specific and tissue-specific resident stem cells that construct the new tissue as stimulated by the bioactive factors secreted by exogenously supplied autologous MSCs [43]. The environmental mileu in the setting of degenerative tendinosis and arthrosis is catabolic. Cartilage and joint homeostasis depend on a balance between anabolic and catabolic features of the biochemical environment. Cell therapy favors anabolism by virtue of the cytokine exchange that occurs during the procedure.

While there was initial excitement and determination that mesenchymal stem cell concentrates injections worked mainly through trophic mechanisms, that concept was abandoned approximately ten years ago. Defining immunologic signaling pathways and deciphering immunomodulatory mechanisms specific to orthopedic tissues has progressed the field significantly and led to broader inquiry into potential mechanisms that account for clinical treatment success. Biologic tissues are subject to convalescence in the aging organism and

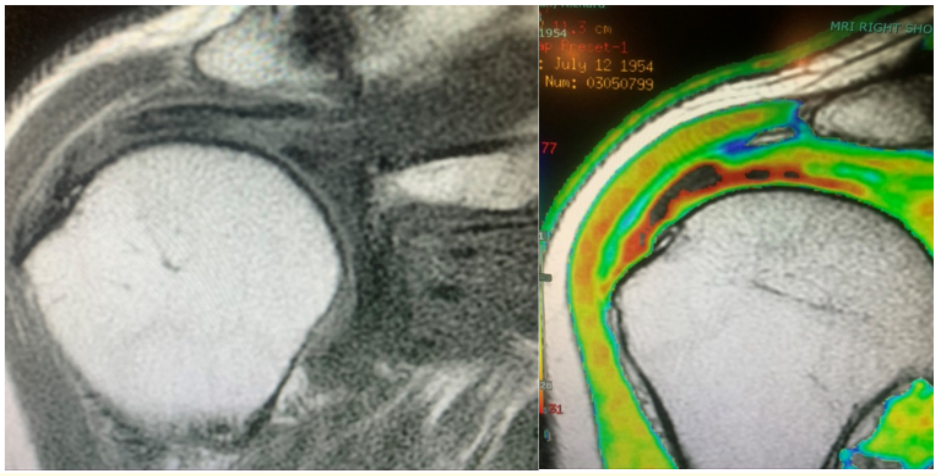

Figure 1: *MRI and MR Cartigram® imaging of articular-sided Intrasubstance PTRCT of supraspinatus tendon at time of presentation.*

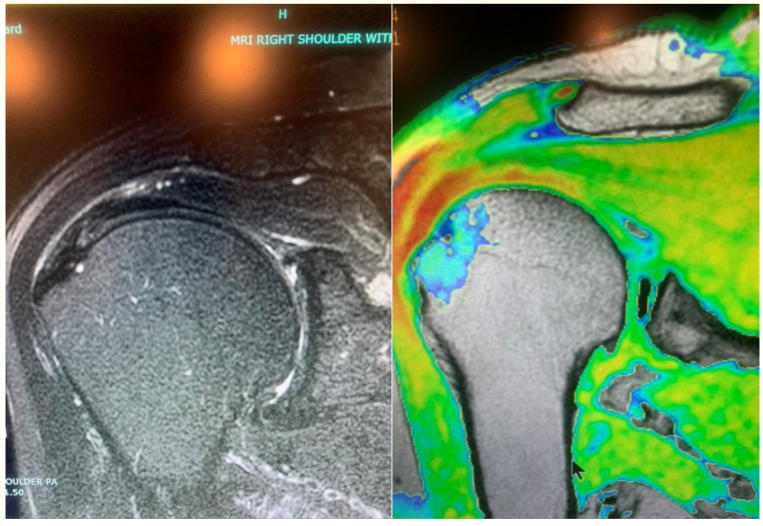

Figure 2: *MR Cartigram® Imaging of healed PTRCT in supraspinatus at one year. Note subchondral response.*

some authors have suggested a role for senolytic compounds and anti-oxidant supplementation plus NAD+ in the setting of cell transplant procedures to enhance the healing environment and promote anti-inflammatory pathways in the biological organism/physical machine.

Protein elaboration by transplanted cells is stimulated by gene products that are activated by environmental factors including paracrine factors and physical deformation of the extracellular matrix through cadherin and integrin deformation. SRY Box Transcription

Factor 9 (SOX9) is a protein coding gene related to the skeletal system that plays a critical role during embryonic development and growth of the organism. The SOX9 protein binds to specific regions of DNA and regulates the activity of other genes and is by definition a transcription factor that is related closely to extracellular signal regulated kinase (ERK) and the wingless related integration site (Wnt) factors. Wnts are secreted factors that regulate cell growth, motility and differentiation. Wnts act in paracrine fashion by activating signaling cascades inside target cells. Both intracellular and extracellular mechanisms with secondary and tertiary messengers are involved in this complex cell signaling process that continues to be deciphered.

Low intensity pulsed ultrasound (LIPUS)

We now provide a handheld personal low intensity pulsed ultrasound (LIPUS) device to all patients with instructions on appropriate use in the post-procedural setting. All living organisms are subject to external physical forces in their environment. The conversion of these physical forces into biochemical signals and integration of these signals into a functional response is termed mechanotransduction. On a cellular level, a mechanical stimulus generates a biochemical signal, which in turn can bring about a number of intracellular processes. These include activation of complex signaling pathways, upregulation or downregulation of gene expression, and alteration of protein synthesis, resulting in adjustment of the intracellular and extracellular environment in response to the initial mechanical stimulus. This mechanosensitive feedback modulates cellular functions as diverse as migration, proliferation, differentiation, and apoptosis, and is crucial for organ development and homeostasis [44]. LIPUS may enhance outcomes in regenerative techniques in orthopedic surgery and further study is indicated.

Post procedure analysis of treatment

Total nucleated cell counts with viability are performed in each patient immediately after the procedure. Patient outcomes are quantified using the SST, the DASH, the SF-12 and VAS for pain in the preoperative setting and at each clinical visit for five years [45,46]. Total nucleated cell count was 3.58 x 107 with a viability of 99% in the case example. Patient outcomes analyses demonstrated marked improvement in all instruments: SST 58% to 97%, DASH 15.8 to 5.0, SF-12 scores were unchanged in this patient, the visual analog score for pain improved from 6 to 2. Enzyme linked immunosorbent assay was used to confirm concentration of TSG-6 with HA in the final GFC product.

Discussion and Conclusion

Despite their high prevalence, ongoing controversy surrounds the best treatment modality for partial thickness rotator cuff tears [47,48]. Partial thickness tears of the rotator cuff are a common cause of clinical morbidity among orthopedic surgery patients, being two or three times more common than full-thickness tears [48]. Both operative and non-operative management of partial thickness tears of the rotator cuff remains controversial in orthopedic surgery. The purpose of this study was to examine a novel technique for treatment of partial thickness rotator cuff tears by leveraging orthopedic biologic techniques to improve tissue health with the ultimate goal of restoring function and eliminating clinical symptoms. Other authors have studied partial thickness tears of the rotator cuff and have provided evidence several baseline predictors of outcome exist in the setting of non-operative care. Laterality, etiology (traumatic versus atraumatic) and thickness of tendon tear (< 50% versus > 50%) have all been shown to play a role in predicting outcome [49]. Importantly, in their study, Lo., *et al*. demonstrated that 76% of partial thickness tears of the rotator cuff did not show progression on anatomic MR imaging. Other authors have suggested that the repair technique, whether *in-situ* or after completion to full-thickness rotator cuff tear, does not significantly affect the outcomes where PTRCTs are concerned, indicating the need for additional inquiry [50]. Additional literature suggests evidence for inferior outcomes and higher failure rates for bursal sided versus articular sided cuff tears [51,52].

Currently, after failure of multi-modality conservative measures, operative intervention is typically indicated for patients with pTRCTs involving more than 50% of the tendon thickness [53]. While debate remains, *in-situ* repair has proven to significantly improve pain and functional outcomes for articular sided and bursal sided tears alike [54]. Studies comparing tendon take-down with reconstruction to *in-situ* repair have shown similar structural and functional outcomes to repair *in-situ* [55]. Most non-overhead athletes are able to return to

sports at the same level of performance. Rates of return to sport for overhead athletes have been generally poor regardless of technique, perhaps indicating these patients as ideal for consideration of using orthopedic biologic techniques to enhance outcomes.

The optimum treatment strategy for partial thickness tears of the rotator is evolving and we believe that in the appropriate setting, orthobiologic management may deserve a spot in the clinician's armamentarium when it comes to managing this disease. Timing of intervention between immediate surgical repair versus delayed repair after six months of nonsurgical treatment has also been investigated [56]. Both approaches resulted in improved clinical outcomes, with a low incidence of re-tears. The authors concluded that at six months post-operatively, superior functional outcomes were observed in the delayed repair group, suggesting a role for preoperative nonsurgical care with no risk of tear progression which may have been due to the enhanced range of motion and motor stability resulting from multimodality conservative interventions applied.

Other authors have similarly used MRI to assess tendon integrity after arthroscopic repair of bursal versus articular sided partial thickness tears, although we are not aware of any literature that promotes the utility of Cartigram® imaging to obtain higher degrees of anatomic information [57,58].

Partial thickness tears of the rotator cuff tendon continue to cause significant morbidity as surgeons continue to look for novel interventions [59]. Who is the ideal patient for management with orthobiologics in partial thickness rotator cuff tears? Healthy patients without metabolic disease, younger age, full shoulder range of motion (with particular attention to internal rotation) normal strength and no cervical disease are likely more ideal candidates for biologic intervention. Patients with smaller, less complex or delaminating type tears may perform better with biologic techniques. Other authors have reported on the use of stem cells and growth factors in rotator cuff tendon repair and reported similar findings [60-63]. This has led some to conclude that patient's own signaling cells are the next generation of medicine [64,65]. Indeed, the improvements in the patients outcomes analysis demonstrate the viability of this technique in the appropriate setting and further research is indicated. Orthobiologic treatments for partial thickness rotator cuff disease are evolving and successful treatment of these lesions clinically and anatomically opens the door for additional inquiry into the potentially broad application of these techniques in PTRCT [66].

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