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The role of biologic agents in the management of common shoulder pathologies: current state and future directions

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The field of orthopedic surgery has seen a rapid increase in the use of various biologic agents for the treatment of common musculoskeletal injuries. Most biologic agents attempt to harness or mimic naturally occurring growth factors, cytokines, and anti-inflammatory mediators to improve tissue healing and recovery. The most commonly used biologic agents are platelet-rich plasma and cells derived from bone marrow aspirate and adipose tissue. These agents have become increasingly popular despite a relative dearth of clinical data to support their use. Much confusion exists among patients and physicians in determining the role of these agents in treating common shoulder pathologies, such as glenohumeral osteoarthritis, rotator cuff tears, and tendinopathy. This article reviews the basic science and clinical evidence for the most commonly used biologic agents in the management of common shoulder pathology.

Keywords: Platelet-rich plasma; bone marrow aspirate concentrate; mesenchymal stem cells; rotator cuff tear; glenohumeral arthritis; rotator cuff impingement

Biologic agents represent an emerging treatment modality for a variety of musculoskeletal conditions. These agents include naturally occurring growth factors and anti-inflammatory mediators that can potentially accelerate tissue healing and recovery. They may act through a variety of mechanisms, including increased angiogenesis, matrix synthesis and remodeling, cell recruitment, and alteration of inflammatory markers and metalloproteinases. Their possible role in pain reduction, tissue healing, and tissue regeneration is of special interest to physicians who treat patients with musculoskeletal injuries.

An important feature of commonly used agents, such as platelet-rich plasma (PRP) and bone marrow aspirate products, is their autologous nature. The most commonly used autologous biologic agents in orthopedic surgery are PRP and cell preparations derived from bone marrow or adipose tissue. Each biologic agent is unique in its protein and cellular composition and its ability to modify the local tissue environment.

Although biologic agents have great promise as an innovative treatment option, their widespread use has outpaced the available clinical evidence. There has been a rapid growth in the number of available agents, with growth

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largely resulting from aggressive direct-to-consumer marketing leading to patient demand rather than robust clinical data. There is an increasing body of basic science studies that support a potential role for these agents in the treatment of various musculoskeletal injuries; however, high-quality clinical data to support their regular use are lacking. It is incumbent on practitioners to understand the landscape of currently available products and the relevant clinical data.

Further confusion is introduced by inconsistent and often poorly understood terminology. Patients often collectively refer to all biologic agents as ''stem cell therapy.'' It should be understood that the number of true stem cells by formal criteria is very small with currently available, minimally manipulated products.[43] This widespread misconception among patients, practitioners, and industry is due to the combination of our currently incomplete understanding of ''biologics'' and the aggressive marketing by both industry and physician practitioners who use potentially misleading advertisements that incorrectly label products as stem cell therapy to attract patients. Physicians must be well educated in the differences between various products and understand the pros and cons of each approach.

Biologic agents have been used to treat a variety of orthopedic conditions, including osteoarthritis (OA), tendinopathy, ligament injuries, and various inflammatory conditions. The shoulder is an area in which biologic agents are especially appealing. Rotator cuff tendinopathy, rotator cuff tears, subacromial impingement, and OA are extremely common upper-extremity injuries with a substantial health care burden. Although not as common as OA of the hip or knee, shoulder OA has been estimated to affect up to 32.8% of individuals older than 60 years.[45,76] Rotator cuff tears occur in over 20% of the general adult population, with a progressively higher incidence as age increases.[17,69,87] The rotator cuff also undergoes a variety of tendinopathic and avascular changes during the aging process, which can result in partial- or full-thickness rotator cuff tears. These tendinopathic changes can lead to reduced intrinsic healing potential following surgical repair, as evidenced by a high rate of healing failure after repair.[20,27,39,88] These chronic changes and poor healing capacity make the rotator cuff an especially appealing target for biologic agents.

This article reviews the role of biologic agents in the treatment of the most common shoulder pathologies, including rotator cuff tendinopathy, rotator cuff tears, and OA. The goals of this review are as follows: (1) to help physicians better understand the appropriate terminology for the most commonly used biologic agents, (2) to review the current literature on the use of various biologic agents in the treatment of the most common shoulder pathologies, and (3) to discuss emerging therapies and potential future applications of biologic agents in the management of these shoulder pathologies.

PRP therapy

Background

PRP is an autologous blood sample that has a higher concentration of platelets compared with baseline whole blood.[14,64] As an autologous blood product, it is rich in growth factors that can potentially modulate the inflammatory pathway and allow improved healing of tendon, ligament, muscle, and bone.[1,12,48,51] The potential for augmented healing and a relatively low risk profile make PRP an especially appealing biologic agent.

PRP is typically prepared by obtaining autologous whole blood from a patient and then completing a 1- or 2-step centrifugation process to separate plasma from leukocytes and red blood cells. The centrifugation process separates and concentrates platelets, which contain numerous cytokines in their alpha granules, including transforming growth factor β, basic fibroblast growth factor, and platelet-derived growth factor, which can stimulate healing and promote growth of muscle and tendon.[24] The potential to deliver a high concentration of various growth factors makes PRP especially appealing in the treatment of rotator cuff tears and tendinopathy given the poor healing capacity of the rotator cuff.

Generally, there are 2 main types of PRP based on the white blood cell concentration: leukocyte-rich PRP (LR-PRP) and leukocyte-poor PRP. Leukocyte-poor PRP contains only the pure plasma layer of the PRP preparation, whereas LR-PRP includes some of the leukocyte-containing buffy coat layer.[52] Although leukocytes are important in wound healing and tissue repair, they may also induce an excessive inflammatory response.[64]

One significant limitation of PRP is the inherent variability in the final composition, which is influenced by numerous factors. Patient-specific factors include age, sex, recent activity level, and recent diet.[94] Preparation-specific factors include the type of collecting tube, centrifugation speed, and number of centrifugation cycles.[4,75] Some studies have even shown a wide variation in PRP composition in separate samples obtained from the same patient.[64] This variety in PRP composition makes it difficult to generalize findings across research studies and is an inherent limitation in the field of PRP research.

Basic science evidence

The clinical use of PRP is largely based on strong in vitro support of its positive effects on tenocytes and myocytes. In vitro studies show that tenocytes exposed to PRP have increased cell proliferation and matrix synthesis, which could potentially lead to improved tendon regeneration or healing.[3,29] Adult tendons also include a small number of tendon stem and/or progenitor cells, which can be induced to active tenocytes by PRP.[98,101] The potential positive effect of platelet-derived factors and the induction of tenocyte

progenitor cells to mature tenocytes in vitro make PRP an especially appealing agent in the treatment of rotator cuff tendinopathy and tears.

Clinical evidence

Although PRP has shown promising results in vitro, the clinical results of PRP in the treatment of various shoulder pathologies have been highly variable. The theoretical ability to reduce pain and induce a more favorable healing environment makes PRP especially appealing in both the nonoperative and operative management of rotator cuff disease. Regarding nonoperative management of rotator cuff disease, PRP has been studied as an alternative to subacromial corticosteroid injections (CSIs). Shams et al[84] conducted a prospective, randomized controlled study to compare subacromial PRP injections vs. CSIs in 40 patients who had symptomatic partial rotator cuff tears. Pain scores and patient-reported outcomes were recorded at 6, 12, and 24 weeks after injection. Both injection groups demonstrated a statistically significant improvement in clinical outcomes compared with the preinjection state. Although PRP showed a statistically significant improvement in outcome and pain scores at 12 weeks, there was no difference between the 2 groups at 24 weeks. This study suggests that PRP may be an appropriate substitute for CSIs, especially in patients for whom corticosteroid therapy is contraindicated. PRP may also have the added benefit of preventing iatrogenic tendon weakening, which is a concern with excessive corticosteroid therapy.[21,30,31] In addition, PRP injections have been investigated in the nonoperative treatment of a variety of tendinopathies, including rotator cuff tendinopathy, with LR-PRP more commonly showing favorable results.[28]

PRP was found to be efficacious in the management of shoulder adhesive capsulitis in a randomized trial performed by Kothari et al.[54] They randomized 195 patients with shoulder adhesive capsulitis into 3 groups receiving either an intra-articular PRP injection, an intra-articular CSI, or ultrasound therapy. Treatment with a PRP injection led to statistically significant improvements over CSI and ultrasound therapy in passive range of motion, active range of motion, pain scores, and patient-reported functional measures at 12 weeks. One significant limitation of this study was the lack of long-term follow-up.

Unfortunately, such encouraging nonoperative results have not been consistently reproduced with PRP injections. Kesikburun et al[46] performed a double-blinded, randomized controlled trial of 40 patients with rotator cuff tendinopathy receiving either PRP or a saline solution placebo injection along with following a physical therapy program. There were no differences between the groups in functional outcome scores or pain scores at any time point within 1 year after injection.

Clinical data to support the role of PRP in surgical management of rotator cuff tears are equally mixed. Despite a growing number of studies showing efficacy in reducing postoperative pain and improving healing rates, results have been tempered by the heterogeneity of these studies.[5,36,68] Studies often differ in underlying tendon pathology, repair technique, postoperative rehabilitation, and PRP composition, making it difficult to make comparisons between studies and to establish firm conclusions.

Multiple studies have shown no benefit of platelet-rich fibrin matrix in the rotator cuff tendon healing rate or functional outcomes.[35,79] However, PRP injections after arthroscopic rotator cuff repair have shown some short-term benefits, including reduced pain and improved functional scores, yet these results have generally not been reproduced with long-term follow-up. Randelli et al[78] performed a prospective, double-blinded, randomized controlled trial investigating clinical outcomes following full-thickness arthroscopic rotator cuff repair with or without PRP injections. Pain scores were lower for the PRP group up to 30 days after surgery, and some outcome scores were significantly higher 3 months after surgery. However, there was no difference in all clinical outcome measures at 6, 12, and 24 months postoperatively. Similarly, a recent prospective randomized study by Malavolta et al[62] reported clinical and structural outcomes following arthroscopic single-row rotator cuff repair augmented with PRP injections with 5-year follow-up. No differences in clinical outcome scores or retear rates were found at any time point up to 5 years after surgery. Verhaegen et al[89] examined the use of PRP after arthroscopic needling of rotator cuff calcific deposits. All patients improved significantly with no difference in rotator cuff defects up to 1 year after the procedure regardless of whether the patient received a PRP injection.

Despite these mixed clinical results, some studies have shown improved healing with decreased rates of failed healing following PRP augmentation of arthroscopic rotator cuff repair. Jo et al[42] showed a significantly lower failure rate (20% vs. 55.6%) and increased supraspinatus cross-sectional area 1 year after PRP injection vs. no injection with repair of large to massive rotator cuff tears. Of note, the speed of healing and the overall clinical outcomes were similar between groups except for overall shoulder function scores at 1-year follow-up. Although studies have shown a decreased rate of incomplete or failed healing following PRP injection, the clinical significance of this is uncertain because many studies have shown that clinical outcome scores do not always correlate with successful rotator cuff healing.[27,44,74,88,93]

Finally, conclusions from systematic reviews and meta-analyses have been mixed when analyzing the role of PRP in surgical management of rotator cuff tears. A meta-analysis by Zhao et al[99] reviewed 8 randomized controlled trials comparing arthroscopic rotator cuff repairs with or without PRP injections. No difference was found in outcome scores or structural healing rates. A more recent systematic review by Hurley et al[35] concluded that PRP injections resulted in improved healing rates for small to

medium rotator cuff tears, improved pain scores, and better clinical outcomes. Their analysis included 18 randomized controlled studies with 1147 patients. Conversely, a meta-analysis by Saltzman et al[81] in 2016 found no difference in clinical outcomes after administration of PRP injections following arthroscopic rotator cuff repair. The heterogeneity in conclusions is likely attributable to the wide variability in patient factors (age, sex, tendon pathology, and medical comorbidities such as smoking and diabetes), type of PRP, and outcome measures used, which illustrates the unclear role of PRP in the current management of rotator cuff tears.

Future approaches for PRP

As previously stated, a major disadvantage of PRP is the variability of composition between patients. To reduce or eliminate this negative feature of PRP, recent efforts have focused on the development of an ''off-the-shelf'' allogeneic PRP product. Allogeneic PRP is particularly appealing because it allows for standardization of PRP preparation and composition. A 2017 study by Kieb et al[47] introduced allogeneic PRP powder as a method to standardize PRP growth factor concentrations. They created lyophilized PRP powder using 12 pooled platelet concentrates from different donors and demonstrated consistently elevated growth factor concentrations compared with whole blood. Theoretically, this preparation of PRP could allow physicians to choose the exact composition of PRP to apply a defined content of growth factors based on the specific tissue being treated.

Jo et al[41] specifically analyzed allogeneic PRP in vitro and in vivo for the treatment of rotator cuff repair. Allogeneic PRP was obtained from 2 healthy donors and screened in a similar fashion to an allogeneic blood transfusion. This preparation method also has the benefit of a known composition, which eliminates the variability seen in autologous harvesting. In their study, human allogeneic pure PRP led to pleiotropic effects on human rotator cuff tenocytes in vitro. Allogeneic PRP injection was then administered to 17 patients with rotator cuff pathology and compared with a matched control group receiving CSIs. Both groups showed significantly improved pain and outcome scores, with CSI showing improvement sooner and PRP showing longer-lasting results up to 6 months. No adverse events were seen after allogeneic PRP administration. Although more rigorous studies are needed, the use of allogeneic PRP appears to be safe and potentially efficacious in preliminary studies.

Other future directions of blood-derived biologic agents include autologous conditioned serum and autologous protein solution. Although there are some emerging basic science data to support the theoretical advantages of these approaches, very few high-quality clinical data are currently available to support their use.

Conclusions

Given the wide variety of clinical results for PRP injections for various shoulder pathologies, expectations must be tempered by clinicians and patients. Although basic science literature supports a potential role in the management of rotator cuff tears, robust clinical data are lacking to support their widespread use. It may be reasonable to consider a PRP injection in patients who have a contraindication for CSIs, in the setting of revision rotator cuff surgery, or in patients who have risk factors for poor healing. Although it has not been directly studied in a clinical setting, PRP may have a role in the management of glenohumeral arthritis given its positive effects on symptoms in patients with OA of the knee.[19,56,85] The positive effect on symptoms of OA is likely due to the presence of anti-inflammatory mediators in PRP. Regardless of the setting or clinical indication, physicians must use PRP with tempered and realistic expectations until more rigorous evidence is available to define the optimal formulations for various conditions.

Cell-based therapy

''Stem cell therapy'' is perhaps one of the biggest catchphrases in the landscape of modern medicine. Aggressive marketing and direct-to-consumer advertising have led to an explosion of interest among the lay public, leading to misguided optimism and often unrealistic expectations. Furthermore, many patients lump all biologic agents into the category of stem cell therapy despite the presence of very few, if any, stem cells in many biologic products. The definition of a stem cell is also complex and often poorly understood. Therefore, patients and physicians alike are often confused about which treatments can accurately be called ''stem cell therapy.''

The definition of a stem cell is complex. Both molecular criteria and functional criteria have been used to define a stem cell. At a minimum, a stem cell must possess the ability for self-renewal and multi-lineage differentiation along various mesenchymal cell lineages, including osteoblasts, adipocytes, and chondrocytes. Minimal criteria defined by the International Society for Cell Therapy include the ability of the cell to adhere to tissue culture plastic, tri-lineage differentiation as noted earlier, and the presence of a specific cell surface marker profile.[22] It should be noted that these minimal criteria were defined for mesenchymal ''stromal'' cells and were described for cultured cells. Therefore, the term ''stem cell'' should not even be used for the minimally manipulated preparations currently available in the United States.

It is critically important to distinguish minimally manipulated cell preparations from laboratory-prepared cell populations that undergo cell sorting and culture expansion. The current regulatory environment in the United States does not permit ex vivo culture expansion, and thus, virtually all ''point-of-care'' autologous preparations used in the United States (ie, bone marrow, adipose, and blood) contain very few true stem cells by formal criteria. In fact,

some authors recommend abandonment of the term ''stem cells'' when using the currently available minimally manipulated cell preparations. Rather, the term ''connective tissue progenitor'' cell has been suggested to be more appropriate. Connective tissue progenitors are defined as a heterogeneous population of tissue-resident cells that can proliferate and generate progeny with the capacity to differentiate into 1 or more connective tissues. These cells are present in many tissues and do have some limited capacity for tissue repair, but they should be distinguished from pluripotent stem cells. Connective tissue progenitors do not possess the characteristics of self-renewal or the ability to reconstitute all the parenchymal cells of the specific tissue.

There are 2 further inherent limitations of most stem cell therapies. First, stem cells may change behavior once they are dissociated from their local environment. Second, the new environment often lacks the appropriate signaling cells or factors to induce differentiation and function of the cells. Therefore, merely transferring cells to a new environment will likely be less effective without the appropriate signaling factors to guide appropriate differentiation and biologic activity at the desired site. It is likely that the principal effect of cell therapy is via a paracrine mechanism, whereby the cells produce soluble factors that affect the biologic activity of local and distant host cells. The transplanted cells may also have an immunomodulatory effect on the local environment.

Autologous sources of stem cells available to clinicians in the United States include cells derived from bone marrow, adipose tissue, and peripheral blood. There is some potential to derive stem cells from umbilical cord blood and amniotic tissues, although robust clinical data on these cell sources are currently lacking. Cells derived from these various sources exhibit some differences in biologic activity and likely have different effects in different target tissues. Furthermore, numerous factors affect the number and biologic activity of cells derived from different tissues, including patient sex, age, and comorbidities.[53] It has become increasingly clear that a much more nuanced and refined definition and characterization of ''stem cells'' is required to optimize the application of cell therapy. The current section will focus on the most commonly used sources of cell-based therapies, bone marrow and adipose tissue, followed by a brief discussion of future directions for cell-based therapy, including leveraging the local stem cell niche and umbilical cord blood cell therapy.

Bone marrow–derived cell-based therapy

Background

Bone marrow aspirate concentrate (BMAC) is an increasingly popular biologic adjuvant with unique advantages. First, it is an autologous product that can be obtained with relative ease at the time of surgical intervention. Second, it contains a small population of mesenchymal stromal cells (MSCs) and progenitor cells, which can potentially facilitate healing.[71] Third, BMAC has been shown to contain more growth factors and up to 3 times more nucleated cells than PRP.[60,100]

BMAC can be easily harvested from multiple sites, including the anterior superior iliac crest or posterior superior iliac crest, proximal humerus, intercondylar notch or distal femur, proximal tibia, and calcaneus.[7,10,97] The iliac crest is often the preferred site of harvest because of its ease of access and superior yield of MSCs compared with peripheral sites.[66] Harvest can be performed at the time of surgery or as an isolated procedure. At least 60 mL of bone marrow aspirate must be harvested to obtain an adequate sample for the concentrated product. Performing multiple small-volume aspirations with small syringes has been shown to result in a 300% increased concentration of progenitor cells compared with single large-volume aspirations.[33] The aspirate is then processed through a series of mesh filters and tubes, followed by centrifugation, until about 6 mL of BMAC is produced for subsequent use.

Preparation and administration of BMAC do not require approval by the US Food and Drug Administration (FDA) if it is processed using only centrifugation (''minimal manipulation'') and used in a homologous manner. This makes it one of the few FDA-compliant procedures that can acquire both progenitor cells and growth factors. However, there are several important drawbacks to BMAC. First, obtaining BMAC is a painful procedure that usually requires some amount of sedation, making it more challenging to use in an outpatient clinic. Second, it requires a harvesting and preparation kit, which increases cost. The most important limitation is that there are a very small number of stem cells by formal criteria in the final cellular composition. Progenitor cells have been found to comprise only 0.001% to 0.01% of total cells in the preparation.[11,63,77] However, BMAC has been shown to have a very high concentration of growth factors, including platelet-derived growth factor, transforming growth factor β, and bone morphogenetic proteins 2 and 7, which have been reported to have anti-inflammatory and anabolic effects.[38,65,83] In addition, some BMAC preparations contain a considerable concentration of interleukin-1 receptor antagonist, which may be instrumental in reducing the local pain response.[92]

Basic science evidence

BMAC has been investigated in the treatment of knee OA, cartilage deficiency, and tendon healing, including rotator cuff healing. Basic science evidence to support the use of BMAC in the management of shoulder pathology is scarce, but there are some promising early data, with most studies analyzing the role of BMAC in rotator cuff healing augmentation. Liu et al[60] investigated supraspinatus tendon healing with PRP and BMAC in a rabbit model. Tendon repairs augmented with BMAC alone or with BMAC and

PRP showed superior biomechanical properties compared with repairs augmented with PRP alone or normal saline solution. BMAC-treated samples demonstrated superior collagen fiber continuity and orientation compared with control samples. BMAC also contained significantly higher levels of several growth factors compared with PRP.

Kim et al[49] studied the effects of BMAC-PRP on tendon-derived stem cells and found that the BMAC-PRP solution enhanced proliferation and migration of tendon-derived stem cells while preventing aberrant chondrogenic and osteogenic differentiation. This finding suggests a possible mechanism for a clinical benefit of BMAC-PRP in the healing of rotator cuff tears.

McDougall et al[67] reported the ultrasonographic appearance of canine supraspinatus tendons with tendinopathy following BMAC-PRP injection. They found that a BMAC-PRP injection was associated with improvements in supraspinatus tendon size, fiber pattern, and echogenicity up to 90 days after injection.

A recent study by Ichiseki et al[37] examined the anti-inflammatory and chondroprotective effects of glenohumeral MSC injections in a rat shoulder arthritis model. Intra-articular injection of MSCs reduced inflammatory markers, increased cartilage protective factors, and inhibited central sensitization of pain. An important limitation of the study was the lack of information on the source of the MSCs. Nonetheless, these results are a promising step and reveal the multifactorial potency of MSCs.

Clinical evidence

Clinical evidence for BMAC in the management of shoulder pathology is limited to a few small case series. Kim et al[48] performed a prospective, nonrandomized, single-blinded study to compare BMAC-PRP injections vs. shoulder exercises in the treatment of partial rotator cuff tears. Twelve patients with a partial rotator cuff tear received a BMAC-PRP injection whereas 12 patients performed rotator cuff exercises alone for 3 months. Pain and functional outcome scores were improved in both groups and were only significantly improved in the injection group at the 3-month time point. Change in tear size did not significantly differ between groups at any time point.

Ellera Gomes et al[26] performed one of the first studies to investigate BMAC and rotator cuff healing. They used BMAC augmentation in 14 patients following mini-open, transosseous suture repair for the treatment of a full-thickness rotator cuff tear. Tendon integrity remained intact in all patients at 1 year after surgery, but 1 patient required revision at 2 years' follow-up. This study was limited by the lack of a control group, but it was one of the first to demonstrate that BMAC could be safely used as an augmentation to rotator cuff repair.

Centeno et al[9] performed a prospective multicenter study investigating results after BMAC injection in 115 patients with glenohumeral OA with or without a rotator cuff tear. Pain and outcome scores were significantly improved at 1 month and up to 2 years compared with pre-injection levels. Although the results are promising, the study was also limited by large heterogeneity in the patient population and the lack of a control group.

The most robust clinical study supporting the use of mesenchymal stem cells in rotator cuff repair was performed by Hernigou et al.[32] A total of 45 patients underwent single-row rotator cuff repair augmented by concentrated mesenchymal stem cells obtained from bone marrow, whereas 45 patients underwent single-row repair without augmentation. Patients treated with concentrated MSCs demonstrated superior tendon healing and enhanced quality of the repaired tendon on magnetic resonance imaging (MRI) and ultrasound. Healing at 6 months was demonstrated by 100% of shoulders in the cell treatment group compared with 67% of shoulders in the control group. Furthermore, at 10-year follow-up, 87% of repairs remained intact in the cell treatment group whereas only 44% of repairs were intact in the control group. Long-term maintenance of tendon integrity was directly correlated with a higher number of implanted cells.

Conclusions

BMAC has the unique advantage of containing a very small population of mesenchymal stem cells and a high proportion of various growth factors, but its true clinical efficacy is still largely unknown. High-quality studies with appropriate control groups are needed to better define its clinical role. A critical deficiency in the current literature is the lack of information correlating the composition and/or biologic activity of marrow-derived cells and clinical outcomes. Furthermore, obtaining BMAC is an expensive procedure with unknown cost-effectiveness. Although BMAC is FDA approved and merits further investigation, its role in rotator cuff repair augmentation is largely unknown at this time.

Adipose tissue–derived cell-based therapy

Background

Adipose tissue is another frequent source for cell harvest. Currently available systems for adipose tissue–derived cell-based therapy produce a stromal vascular fraction, which is a heterogeneous cell population that includes mature adipocytes, fibroblasts, endothelial cells, and adipose-derived stem cells.[95] Enzymatic digestion followed by subsequent culture expansion is required to isolate the desired population of adipose-derived stem cells, but such ''manipulation'' is currently not allowed by the FDA.

Basic science evidence

Adipose-derived MSCs have been frequently investigated in various animal models focused on tendon healing, with mostly favorable results. Lee et al[58] reported the effects of

implanted human adipose-derived MSCs in rats with iatrogenic Achilles tendon injury. Transplantation of human adipose-derived MSCs led to improved biomechanical healing and expression of human-specific type I collagen and tenascin C for at least 4 weeks after implantation, suggesting that transplanted MSCs may be able to differentiate into the tenogenic lineage while contributing their own proteins to tendon healing.

Rothrauff et al[80] investigated the effects of adipose-derived MSC injection following rotator cuff repair in a rat model. Adipose-derived MSCs increased the bone mineral density of the proximal humerus in the setting of chronic rotator cuff tears but not acute rotator cuff tears. The MSCs did not enhance the histologic appearance or structural properties in either acute or chronic tears. Oh et al[72] applied adipose-derived MSCs following rotator cuff repair in a rat model and found increased load to failure, increased compound muscle action potential, and decreased fatty infiltration of the muscle in the MSC-augmented repair group compared with a group with isolated repair and a group with isolated MSC injection. Conversely, Mora et al[70] found no significant differences in supraspinatus tendon biomechanical properties after rotator cuff repair augmented with adipose-derived MSCs. There was also no difference in histologic collagen orientation, but the MSC group did show less histologic evidence of inflammation.

Clinical evidence

Although adipose-derived mesenchymal stem cell therapy is largely considered investigational at this stage in its development, a few clinical studies have investigated its efficacy in treating various shoulder ailments. Recently, Jo et al[40] reported a clinical study investigating the effects of an intratendinous injection of autologous adipose-derived MSCs in patients with partial-thickness rotator cuff tears. Medium- and high-concentration injections resulted in significantly reduced shoulder pain, improved clinical outcome scores, and an up to 90% reduction in the bursal-sided defect on follow-up MRI. This study was limited by the small patient population (20 patients) and lack of a control group. Nonetheless, the possibility of inducing neotissue formation in a partial rotator cuff defect without surgery is promising.

Kim et al[50] investigated clinical and MRI outcomes following rotator cuff repair augmented with adipose-derived MSCs loaded in fibrin glue. In their study, 35 patients received MSC injections and were compared with 35 matched control patients who did not receive injections. At 2 years postoperatively, both groups significantly improved compared with preoperative levels, but there was no difference in clinical outcomes between the groups at 2 years, including pain, range of motion, and functional outcome scores. A significantly lower rate of failed healing in the MSC group (14.3%) compared with the control group (28.5%) was found on 1-year follow-up MRI. This study suggests that MSCs may safely increase postoperative rotator cuff healing yet clinical outcomes may not be similarly improved despite the increased healing rate.

Future approaches to use of cell-based therapy

The field of cell-based therapy is rapidly evolving as new technology emerges. One promising frontier for cell-based therapy is the ability to leverage the intrinsic stem cell niche. It is well established that many tissues harbor a small population of intrinsic progenitor cells that are associated within the walls of blood vessels. These cells are normally quiescent but can potentially be stimulated during tissue injury and repair. For example, Eliasberg et al[25] reported decreased rotator cuff fatty atrophy following rotator cuff repair augmented with perivascular MSCs in a murine model. It is believed that the local microenvironment may contain the necessary signaling factors to induce biologic activity of these cells in the setting of tissue injury and repair. Recently, the subacromial bursa has been identified as a local source of mesenchymal stem cells in the shoulder.[23,59,86] Harnessing these intrinsic stem cells would be an alternative approach to the use of exogenous cell sources. The current challenge is to identify methods to stimulate the intrinsic stem cell niche.

Umbilical cord blood is another emerging source of MSCs owing to its ease of availability, high proliferation capacity, and low immunogenicity.[57,91] Kwon et al[55] investigated the effect of umbilical cord blood–derived MSCs on chronic rotator cuff tears in a rabbit model. Compared with controls, rabbits injected with MSCs demonstrated newly regenerated type I collagen fibers, improved cell proliferation, angiogenesis, and an improved walking distance and mean walking speed. Similarly, Park et al[73] reported the regenerative effects of a single human umbilical cord blood MSC injection in rabbits with full-thickness subscapularis tears. Injection alone resulted in partial healing with predominantly type I collagen in 7 of 10 rabbits.

There are multiple other avenues that attempt to manipulate the local stem cell environment but require further research before clinical application. These include manipulation of local angiocrine factors produced by tissue-specific endothelial cells, induced pluripotent stem cells, and gene therapy approaches. At this point, these therapies are considered experimental, with minimal to no clinical data to support their use.

Conclusions

Cell therapy represents a promising approach for the treatment of symptoms associated with shoulder impingement, rotator cuff tears, and glenohumeral OA. Furthermore, there is emerging evidence of the potential for clinically meaningful tissue regeneration and healing.

Further basic science and clinical evidence is needed to define the role of cell therapy in treating various musculoskeletal pathologies. Physicians should continue to use discretion when considering the use of cell therapy, and special attention should be given to preparation methods that ensure compliance with ethical and legal standards.

Other options to manipulate biology in shoulder

There are a variety of other biologic and nonbiologic approaches that are readily available and can also be useful in the management of shoulder pathology. Pharmacologic therapy that maximizes a patient's ability to heal must be considered depending on the patient's medical comorbidities. For example, orthopedic surgeons should focus on identifying and optimizing factors with known negative effects on rotator cuff healing prior to surgical management of a rotator cuff tear. Poor glucose control, osteoporosis, hypercholesterolemia, vitamin D deficiency, smoking, and the use of nonsteroidal anti-inflammatory drugs have all been associated with impaired rotator cuff healing.[2,6,13,15,16,18,82,96] Every effort should be made to manage and reduce these risk factors prior to primary or revision rotator cuff repair. A primary care physician or endocrinologist can be especially helpful in the management of diabetes mellitus, osteoporosis, and smoking cessation. Sometimes pharmacologic intervention can be beneficial, especially in the management of hyperglycemia or poor bone mineral density. For example, hyperglycemia has been shown to be detrimental to rotator cuff healing in a rat model.[6] Certain medications, such as vitamin D and recombinant parathyroid hormone, have also been shown to have a positive effect on rotator cuff healing in preclinical studies.[2,34] Similarly, low-intensity pulsed ultrasound has been shown to improve the histologic appearance of rotator cuff tendon-bone integration and increase bone mineral density at the cuff insertion site.[61]

Another approach to healing augmentation is the use of extracellular matrix materials (commonly referred to as a ''patch'') as a scaffold to support tendon healing. These patches have been advocated for use in managing partial-thickness rotator cuff tears and augmentation of large, full-thickness rotator cuff repairs. There are 2 proposed biomechanical mechanisms for improvement in healing. First, the patch may act as a load-sharing device that can help reduce peak strains across a partial rotator cuff defect or a repaired tendon. Second, the patch may serve as a scaffold to support cell attachment and new matrix synthesis. An extracellular matrix patch may facilitate new tissue formation by providing a supportive scaffold.[8,90] A study by Bokor et al[8] reported 2-year outcome results in 12 patients with partial rotator cuff tears treated with collagen patch augmentation. New tissue formation was seen in all patients as early as 3 months postoperatively. This tissue matured over time and became indistinguishable from normal rotator cuff tissue on MRI, with complete healing in 7 of 12 patients. No tear progression was seen in any patient, and clinical scores were improved in all patients at 2-year follow-up.

Conclusion

The landscape of biologic agents in orthopedic surgery is rapidly changing. Physicians must maintain a thorough understanding of the growing literature to identify the optimal indications for use of various biologic agents, as such evidence can help guide clinical decision making. Autologous biologic agents vary in ease of acquisition, in composition, and likely in effectiveness for treating a variety of shoulder pathologies. PRP is relatively easy to harvest, with heterogeneous clinical results despite strong basic science support for its use. Cell therapy approaches, including use of BMAC and adipose-derived cells, also have promising basic science evidence but few clinical studies to support their regular use. A critical limitation currently is the inability to isolate and expand via cell culture the very small number of ''stem cells'' found in these various autologous preparations. It appears that implanted cells act via a paracrine mechanism whereby they produce soluble factors that stimulate local host cells, suggesting the possibility of harnessing the small population of intrinsic progenitor cells that are resident in many tissues. Finally, physicians should not neglect nonbiologic agents when treating patients with shoulder pathology.

Above all else, orthopedic surgeons must be well informed when discussing biologic agents with patients. The combination of aggressive marketing and patient demand has led to the indiscriminate use of cell therapy for a wide range of musculoskeletal conditions in the United States. It is paramount that orthopedic surgeons provide leadership in this area and work toward developing practice guidelines and policies for the use of biologic agents. A rigorous approach to the use of ''regenerative medicine'' therapies and the maintenance of high clinical and research standards are required to move the field forward.

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