The Use of Biological Approaches in the Treatment of Shoulder Pathology

A Critical Analysis Review

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Abstract

» The major pathological conditions affecting the shoulder that are treated with use of biological applications include focal cartilage lesions and rotator cuff tears. Biological modalities that previously have been used or investigated include platelet-rich plasma (PRP), growth factors, progenitor cells, bone-marrow stimulation, autologous chondrocyte implantation (ACI), matrix-induced ACI (MACI), and biological scaffolds.

» Marrow-stimulating procedures have been reported to yield positive results when used for the treatment of focal cartilage lesions of the glenoid or humeral head. Limited data are available on the use of PRP, ACI, and MACI for the treatment of chondral lesions involving the shoulder, and therefore no conclusions can be drawn regarding the efficacy of these modalities.

» Preclinical and in vitro studies have demonstrated that modulation of growth factors may be helpful for rotator cuff tear healing; however, the optimal modulation and delivery vehicle remain to be elucidated. PRP has received much research attention; however, most studies have been hindered by study setup and conflicting results. Therefore, the use of PRP to enhance rotator cuff healing remains controversial. Progenitor cells have shown positive results in a small number of preclinical and clinical studies, but further research is needed before conclusions can be drawn.

» In summary, basic-science studies investigating biological factors to enhance healing in the shoulder have shown potential. However, clinical data are still limited, contradictory, and controversial. Additional research is needed. Most importantly, robust, consistent, well-powered clinical trials are necessary to definitively determine which methods improve clinical outcomes.

Shoulder pain is the second most common musculoskeletal complaint encountered in primary care offices, occurring in about 51% of patients[1]. Over the last few years, major advances have been made in both the operative and nonoperative treatment of shoulder pain and pathological conditions. However, because of increasing patient age and the rising number of active patients, there is a demand for improved treatment of all shoulder abnormalities. Therefore, the use of orthobiologics in shoulder surgery has expanded rapidly over the past decade. Some of the commonly used biologics in shoulder surgery include

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progenitor cells, growth factors, platelet-rich plasma (PRP), and biological matrices. The potential advantages of biological augmentation of traditional shoulder surgical techniques include minimal invasiveness, improved healing capacity, and more-rapid recovery. Conversely, the use of biologics is currently expensive, and the evidence of long-term effectiveness is limited. Furthermore, the body of literature on the use and efficacy of biologics in shoulder surgery is heterogeneous with regard to indications, therapies, processing methods, and inoculation. Although some studies have demonstrated encouraging results following either isolated treatment with biologics or biologic-augmented surgery, other studies have failed to demonstrate substantial benefit. Given the heterogeneity and paucity of critical analyses within the literature, the objective of the present review is to evaluate the value of orthobiologics in the treatment of shoulder pathologies. More precisely, we aim to perform a balanced evaluation of biologic augmentation of existing modalities for the treatment of focal chondral defects, osteoarthritis, and rotator cuff tears.

Focal Chondral Defects and Glenohumeral Osteoarthritis

A trial of conservative therapy consisting of physical therapy and nonsteroidal anti-inflammatory medications is typically seen as the primary treatment when a symptomatic cartilage defect is identified in the shoulder[2]. If symptoms persist, biologic-based treatments such as marrow-stimulation procedures, bone marrow aspirate concentrate (BMAC), PRP, and cell-based therapies such as autologous chondrocyte implantation (ACI) or matrix-induced ACI (MACI) can be used.

Microfracture

The microfracture procedure has been widely used in several joints because of its ease of performance, low cost, and overall positive reported outcomes when used for the treatment of small, contained cartilage lesions. The aim of this technique is to perforate the subchondral bone to promote the release of progenitor cells and multiple growth factors to the chondral defect. Under favorable mechanical-stress characteristics (stress-free joint movement with varying pressure, tensile, and shearing forces), these progenitor cells will differentiate into fibrochondrocytes, ultimately creating a fibrocartilage layer. However, the higher content of type-I collagen makes this repair tissue one of lesser biomechanical quality than hyaline cartilage, as previously reported in animal experiments[3]. Patient selection is most certainly key for successful outcomes. However, clear indications are not available in the shoulder literature; therefore, on the basis of an algorithm that has been extrapolated from the knee literature, microfracture is considered to be suitable for the treatment of small, circumscribed cartilage defects (maximum, 4 cm^2) with intact subchondral bone in young, active patients[4-7].

In general, better results have been reported for small unipolar defects on either the glenoid or humeral side, whereas the worst results have been seen in association with bipolar glenohumeral lesions[2,3,8]. Millett et al., in a study of 31 shoulders, reported significant ($p < 0.05$) reduction in pain and improvement in function according to the American Shoulder and Elbow Surgeons (ASES) score[9] at a mean of 4 years after the use of microfracture for the treatment of full-thickness articular cartilage injuries. Only 19% of the patients in that cohort were considered to have had a failure requiring additional surgery[2]. Likewise, Frank and colleagues, in a series of 16 patients (17 shoulders), reported significant improvement in shoulder function as demonstrated by an increase in the Simple Shoulder Test (SST) and ASES scores ($p < 0.01$ for both) and significant pain reduction ($p < 0.01$) at >2 years postoperatively[10]. Outcomes did not significantly vary with respect to sex or age. Of note, 93% of the patients stated that they would have the surgery again. Last, Siebold and colleagues[11] reported significant improvements in pain and functional scores ($p = 0.0053$ and $p = 0.018$, respectively) in patients managed with microfracture combined with a periosteal flap. Poor prognostic predictors included prior surgery and, potentially, lesion size, although the results were not significant.

Platelet-Rich Plasma (PRP)

PRP has been widely utilized for the treatment of various musculoskeletal conditions or as an augmentation tool on the basis of basic-science and emerging clinical studies[12,13]. The biological reasoning behind the clinical use of PRP includes local delivery of growth factors, modification of the inflammatory response, increased hemostasis, and positive effects on cell proliferation and differentiation[14-17]. Although symptomatic relief has been reported following the use of PRP for the treatment of early-stage knee osteoarthritis[14], we are not aware of any studies that have evaluated the efficacy of PRP in the shoulder. However, autologous platelet-poor plasma and platelet gel have been shown to reduce pain scores and to yield significantly better functional outcomes (internal rotation, $p < 0.05$) following total shoulder arthroplasty[18]. In the study by Lo et al.[19], 55 patients with glenohumeral arthritis were managed with a biologically based resurfacing arthroplasty with use of acellular human dermal allograft in combination with PRP. After an average duration of follow-up of 60 months, the average ASES score was 76 ± 22, the average Western Ontario Osteoarthritis of the Shoulder (WOOS) index was 76% ± 22%, and the average visual analog scale (VAS) score for pain was 2.4 ± 2.6, with an 81% rate of patient satisfaction. The average joint space increased from 1 ± 1 mm preoperatively to 2 ± 1 mm postoperatively. Fewer than 10% of the patients underwent revision to total shoulder arthroplasty.

Autologous Chondrocyte Implantation (ACI) and Matrix-Induced ACI (MACI)

The principle of these techniques is to culture autologous cells and then to implant these cells into the chondral defect[20]. These procedures can be performed with or without a 3-dimensional biocompatible scaffold. ACI and MACI are staged procedures in which an initial arthroscopic harvest is performed to obtain chondrocytes for culture. The chondrocytes are then expanded in culture to obtain 15 to 20 million cells. This expansion takes approximately 1 month, and the cells are then implanted into the chondral defect. There is a paucity of data in the orthopaedic literature on the use of ACI for the treatment of chondral defects within the shoulder. We are aware of only a single case in which ACI has been used for the treatment of a shoulder defect; in that report, a 16-year-old male athlete with a full-thickness lesion (3.3 × 1.5 cm) of the humeral head reported functional improvements at 12 months[21].

For the MACI procedure, a few days prior to implantation, a biodegradable scaffold is seeded with the expanded chondrocytes, which can then synthesize extracellular matrix components[21]. We are aware of only 1 small report on the use of this procedure in the shoulder[22]. In that study, 4 young adults were managed with ACI for the treatment of symptomatic, isolated, large-diameter lesions of the cartilage involving the humerus (3 patients; defect size, 6 cm^2) or glenoid (1 patient; defect size, 2 cm^2). After a mean duration of follow-up of >3 years, the mean pain and functional scores were considered satisfactory (VAS score for pain, 0.3 of 10; Constant score, 83.3 ± 9.9; and ASES index, 95.3 ± 8.1). Moreover, the coverage of the defect on magnetic resonance imaging (MRI) also was deemed satisfactory, with signs of fibrocartilaginous repair tissue.

Rotator Cuff Tears

A number of novel approaches have been described to enhance the biological healing of the rotator cuff repair site, to improve the regeneration of the native cuff insertion site, and to inhibit the formation of scar tissue[23,24]. These approaches include tissue engineering, cell therapy, and growth factors.

Marrow-Venting Procedures

Bleeding bone surfaces, such as those brought about by venting of the greater tuberosity or acromioplasty, can enable the release of growth factors, which can in turn lead to improved cuff healing[22,25]. These factors, including platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), induce inflammation and angiogenesis. Meanwhile, other growth factors improve matrix synthesis, cellular proliferation, and cellular differentiation (transforming growth factor-beta [TGF-β]), promote osseous incorporation of tendon (bone morphogenetic proteins [BMPs]), and remodel the extracellular matrix (matrix metalloproteinases [MMPs])[26]. Gotoh et al., in a study of 24 patients with or without a retear following rotator cuff repair, found increased levels of MMP-3 and tissue inhibitor of MMP (TIMP)-1 in the retear group and concluded that these findings may suggest a potential approach for targeted drug therapy following rotator cuff repair[26]. While there have been no studies investigating rotator cuff healing following treatment with recombinant growth factors in humans, the results of preclinical studies have indicated that the delivery or modulation of these factors may augment rotator cuff healing[27,28]. Bedi et al., on the basis of their findings in a rat model, reported that MMP-13 activity modulation with doxycycline following rotator cuff repair may offer a novel biological approach to improve tendon-to-bone healing[29]. However, the clinical translation of these in vitro and animal studies remains a challenge.

Microfracture

Microfracture of the greater tuberosity, immediately lateral to the rotator cuff repair site, results in extravasation of mesenchymal stromal cells (MSCs), platelets, and growth factors. However, several studies have shown mixed results. Osti et al., in a randomized controlled trial of 57 patients who underwent arthroscopic rotator cuff repair, demonstrated that microfracture of the rotator cuff footprint resulted in reduced short-term pain but did not result in significantly different long-term clinical or radiographic outcomes[30]. Milano et al., in prospective randomized study of 80 patients who underwent arthroscopic rotator cuff repair with or without greater tuberosity microfracture, found no significant difference between the groups on MRI evaluation; however, patients receiving microfracture for large tears demonstrated significantly improved healing rates ($p = 0.040$)[31].

Platelet-Rich Plasma (PRP)

The use of PRP as a biological adjuvant to enhance the healing of rotator cuff tendons has recently increased in popularity, which in turn has led to a number of published studies. PRP is a term that is used to describe preparations of whole blood enriched with platelets that, once activated, release a host of growth factors that may contribute to tissue repair. Several proteoglycans (decorin, aggrecan, and biglycan) have been shown to stimulate the production of key extracellular matrix proteins and to increase proliferation of rotator cuff-derived tenocytes[32]. Moreover, PRP inhibits the inflammatory effects of interleukin-1β (IL-1β), which contributes to rotator cuff tendon degeneration, and heightens levels of TGF-β, which increases rotator cuff tendon repair strength[33,34]. However, these in vitro results have not translated into clinical effects; controversial results have been reported following clinical trials involving the use of different PRP formulations to enhance rotator cuff repairs[32,35-43].

Multiple studies have documented significantly improved results in association with the use of PRP augmentation. Pandey et al. evaluated 102 patients who underwent rotator cuff repair with or without moderately concentrated PRP

and were followed for a minimum of 2 years[44]. At 24 months, the PRP group demonstrated a significantly lower retear rate than the control group (3.8% compared with 20%; $p = 0.01$). The difference in retear rates, however, was significant only for large tears ($p = 0.03$). Doppler ultrasound demonstrated that the PRP group had significantly ($p < 0.05$) increased vascularity of the repair site at 3 months postoperatively and in the peribursal tissue until 12 months[44]. In addition, the PRP group demonstrated significantly improved University of California-Los Angeles (UCLA) scores at 12 months postoperatively ($p < 0.05$) and significantly improved Constant scores at 24 months postoperatively ($p < 0.05$). Jo et al., in a randomized controlled trial, reported a significantly lower retear rate among patients who received PRP than among those who did not (3.0% compared with 20.0%; $p = 0.043$)[45]. Additionally, the supraspinatus cross-sectional area was significantly larger in the PRP group ($p = 0.014$); this finding led the authors to conclude that the quality of postoperative tendon healing is increased by the use of PRP. Of note, the speed of healing and the functional outcomes were equivalent between the 2 groups. Holtby et al., in a retrospective study of 82 patients who were followed for 6 months after the repair of small to medium-sized rotator cuff tears, reported transient improvements in perioperative pain control when comparing the PRP group with the control group[46]. Moreover, neither patient-oriented outcome measures nor structural integrity of the repair significantly differed between groups.

The varying protocols and conflicting results of studies investigating PRP in the setting of rotator cuff repair have led to numerous meta-analyses to further evaluate the data[12]. Warth et al., in an analysis of 11 Level-I and II studies, found that clinical outcomes did not differ between patients who received PRP and controls[13]. The authors reported that placing the PRP at the tendon-bone interface rather than over the surface of the repaired tendon was associated with an overall increase in the Constant score. Additionally, a subgroup analysis of patients who underwent double-row repair for the treatment of large (>3-cm) rotator cuff tears showed significantly lower retear rates in association with PRP use ($p = 0.046$). Vavken et al. performed a cost-effectiveness analysis and meta-analysis of 13 published studies on the use of PRP for the repair of small and medium-sized rotator cuff tears. In contrast to Warth et al.[13], the authors found reduced retear rates following the arthroscopic repair of small and medium-sized rotator cuff tears when patients who had been managed with PRP were compared with controls[47]. However, for large and massive tears, there was no decrease in the retear rate in association with PRP. Cost analysis indicated that, with the current cost, the use of PRP was not cost-effective. Chahal et al., in a systematic review, also noted a reduction in retear rates for small and medium-sized rotator cuff tears[48]. Most recently, Saltzman et al., in a meta-analysis of available review studies, found that the use of PRP for rotator cuff repair did not result in significantly lower overall retear rates or improved clinical outcome scores[49]. Subgroup analysis showed evidence of improved outcomes in association with solid as compared with liquid PRP matrix, small or medium-sized tears as compared with large or massive tears, PRP application at the tendon-bone interface as compared with over the tendon, and in the setting of double-row as compared with single-row repair.

Because of inconsistent clinical results, the use of PRP to improve postoperative rotator cuff healing continues to be an area of debate. Additional randomized clinical trials and basic-science studies are needed to determine the optimal formulation of PRP to improve physiological healing.

Progenitor Cells

The use of multipotent MSCs has become an area of growing interest. Specifically, adipose-derived stem cells (ADSCs) and bone marrow-derived stem cells (BMSCs) can proliferate and differentiate into multiple musculoskeletal tissues, such as tendon, ligament, cartilage, bone, and fat. Interestingly, recent articles have demonstrated the presence of stem cells obtained from bursal tissue. Of note, when treated with BMP-12, these cells expressed markers of tenocytes; therefore, BMP-12 potentially could be an important target in the treatment of rotator cuff degeneration[50,51].

While preclinical studies have demonstrated promising results[52-54], there is still a paucity of clinical studies. Only 2 clinical studies have shown the efficacy of BMSC injections in the shoulder[55,56]. Ellera Gomes et al. reported on 14 patients in whom full-thickness rotator cuff tears were repaired with transosseous sutures with use of a mini-open approach and subsequently augmented with 10 mL of BMSC concentrate, which was injected into the repaired tendon edges[55]. After 12 months of follow-up, MRI examinations demonstrated intact tendons in all patients. Additionally, Hernigou et al. evaluated the 10-year results for 90 patients who underwent single-row rotator cuff repair with (45 patients) or without (45 patients) augmentation with concentrated BMSCs[56]. Intact tendon was found in 87% of the patients in the BMSC group, compared with only 44% of those in the control group.

Adipose tissue represents an abundant and reproducible progenitor cell source as ADSCs can be easily harvested from it. We are aware of only 1 study, involving a rabbit model, which has verified the positive rotator-cuff healing effects of ADSCs[54]. The authors demonstrated that muscle function and tendon integrity were improved following local administration of ADSCs after cuff repair. Additional preclinical and clinical studies are necessary to elucidate the optimal utilization of progenitor cells to enhance tendon healing.

Scaffolds

An area of recent interest in research is the development of new ways to produce synthetic, degradable scaffolds that

TABLE I Grades of Recommendations for Clinical Care*†

	Microfracture	PRP	ACI/ MACI	Progenitor Cells	Bone-Marrow Venting	Scaffolds
Focal chondral defects	Grade B	Grade I	Grade I	Grade I	Grade I	NA
Diffuse osteoarthritis	NA	Grade C	NA	Grade I	NA	NA
Rotator cuff repair	Grade C	Grade C	NA	Grade I	Grade I	Grade I

*Grade A indicates good evidence (Level-I studies with consistent findings) for or against recommending intervention. Grade B indicates fair evidence (Level-II or III studies with consistent findings) for or against recommending intervention. Grade C indicates conflicting or poor-quality evidence (Level-IV or V studies) not allowing a recommendation for or against intervention. Grade I indicates that there is insufficient evidence to make a recommendation. †PRP = platelet-rich plasma, ACI = autologous chondrocyte implantation, MACI = matrix-induced autologous chondrocyte implantation, and NA = not applicable.

reproduce the function and structure of the rotator cuff tendon. Notable advances include the recent development of 3-dimensional electrospun scaffolds that closely resemble extracellular matrix. In addition, coating and fabrication techniques that facilitate the integration of bioactive molecules, including growth factors, within scaffolds have been developed[57,58]. Although these scaffolds are not ready for human implantation at this time, collaboration between researchers focusing on cell biology, biomaterial science, and tissue engineering may lead to scaffolds with the requisite characteristics to initiate rotator cuff tendon regeneration. Other recently developed types of scaffold for the augmented repair of massive rotator cuff tears or the replacement of irreparable cuff tissue are human acellular dermal allograft[59,60] and xenograft[61]. In addition to biomechanical strengthening of the tendon tissue, the rationale behind these techniques is to render the graft acellular, decreasing its immunogenicity, while leaving an intact collagen extracellular matrix; the intact matrix thereby promotes growth of new host tissue into the graft[62]. Short-term results after 24 months of follow-up have been promising[59,61-63]; Barber et al., for example, in a randomized prospective trial, demonstrated superior outcome scores and a lower failure rate with augmented compared with non-augmented rotator cuff repairs[62]. However, further studies are necessary to evaluate the long-term benefits of human acellular dermal scaffolds.

Conclusions

In summary, basic-science studies investigating biological factors to treat chondral defects or enhance rotator cuff healing show promising results. However, clinical data are still limited by inconsistency and controversy, and recommendations for clinical care are not possible (Table I). For focal chondral lesions of the glenoid or humeral head, microfracture has been reported to yield positive postoperative results in the intermediate to long-term follow-up period. The use of PRP, ACI, and MACI treatments for shoulder chondral lesions also has been reported; however, no conclusions can be drawn concerning the efficacy of these modalities. For rotator cuff tear healing, animal and basic-science studies have demonstrated that modulation of growth factors and progenitor cells may be helpful, but the optimal modulation and delivery vehicle remain to be elucidated. Conflicting results have been reported about the role of PRP as biological augmentation for rotator cuff repairs, making this subject an area of continuing debate. In general, additional clinical trials are necessary to elucidate the ideal biological approaches to improve the healing of a variety of musculoskeletal tissues.

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