



# Biologics to Improve Healing in Large and Massive Rotator Cuff Tears: A Critical Review

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**Abstract:** Large and massive rotator cuff tears have the highest risk of retear. Common biologic modalities that can potentially reduce the retear rate and improve healing include platelet-rich plasma (PRP), scaffolds, and mesenchymal stem cells (MSCs). PRP has been studied for its role in improving rotator cuff healing and results of randomized controlled trials and meta-analyses show mixed results. Most studies in large and massive tears show that PRP decreases the retear rate, but the connection between structural integrity and clinical outcomes is still unknown. Extracellular matrix (ECM) and synthetic scaffolds can increase healing in augmentation and bridging repair. Acellular dermal allografts have shown better healing rates and outcomes than xenografts in meta-analyses. Synthetic scaffolds augmented with bone marrow-derived stem cells have only been studied in vitro but are promising for the combination of mechanical stability and induction of a biological response. Superior capsule reconstruction is an exciting type of interposition graft reconstruction that has shown favorable early clinical outcomes for large and massive tears. Bone marrow-derived stem cells and adipose-derived stem cells improve the biomechanical characteristics of tendon repair and enhance the histological findings of the healing process in animal studies. However, evidence from human studies is lacking, especially in patients with large and massive tears. In summary, there are many biological options to augment rotator cuff repair in patients with large and massive tears. Due to mixed results and a lack of standardization in high-quality studies, we cannot recommend PRP at this time as an adjunct to rotator cuff repair. Both ECM and synthetic scaffolds, as well as SCR, can be used, especially in situations where native tendon is compromised, and additional mechanical augmentation is needed. Stem cells have been the least studied to date, so it is difficult to give recommendations for or against their use at this time.

**Keywords:** biologics, large rotator cuff tears, massive rotator cuff tears, platelet-rich plasma, scaffolds, mesenchymal stem cells

## Introduction

The surgical management of large and massive rotator cuff tears poses technical and biologic challenges to the treating surgeon. Many patients with tears of this size suffer from chronic sequelae, such as tendon retraction and tendon loss, as well as muscle atrophy and fatty infiltration of the muscle, all of which create a technically difficult and biologically challenging environment for successful repair.<sup>1</sup> At the tissue level, the biological environment becomes compromised as chronically damaged rotator cuff tendon suffers from reduced cellularity and vascularity, greater collagen disorganization, and lower collagen concentration.<sup>2</sup> Even after surgery, repaired tissue undergoes reactive fibrosis, which contributes to the lack

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of healing and high rates of structural failure or retears.<sup>3,4</sup> Recent reports of structural failure rates after arthroscopic repair of large and massive rotator cuff tears can be up to 94%,<sup>5</sup> with massive tears comprising 80% of recurrent tears.<sup>6,7</sup> While patients can do well clinically, retears are associated with less satisfactory outcomes and the need for additional procedures.<sup>8</sup>

The biomechanics of rotator cuff repair have been studied extensively over the last two decades and in many cases have been improved through better surgical techniques and better repair constructs.<sup>9–11</sup> In order to optimize the integrity of healing and to reduce structural failure, researchers more recently have started to focus on improving the healing environment by modifying the biology following rotator cuff surgery.<sup>12</sup> Biologic adjuvants such as PRP, scaffolds, and stem cells have been investigated as a means to enhance healing at the tendon-to-bone interface and to improve muscle and tendon quality. Since large and massive rotator cuff tears are the most challenging tear pattern to treat, it is in this patient population that biologics could potentially help to enhance healing and improve structural integrity. In this paper, we aim to provide an overview of the most common biological augmentation options and to evaluate the most recent and highest quality evidence on their effectiveness in the treatment of large and massive rotator cuff tears.

## Platelet-Rich Plasma (PRP)

PRP is a whole blood fraction containing high platelet concentrations that, when activated, releases growth factors to aid in tissue repair.<sup>13</sup> The current literature discusses a wide variety of biological adjuvants to augment healing, and PRP has been studied both for its potential benefits in augmenting surgery and in non-operative management. For example, PRP can stimulate tendon to bone healing due to its high concentrations of growth factors that work to influence cell migration, tissue maturation,<sup>14</sup> and inflammation.<sup>15</sup> Specifically, TGF- $\beta$ 3 increases rotator cuff repair strength by decreasing the production of IL-1 $\beta$  in diseased human tissue and diminishes IL-1 $\beta$ 's pro-inflammatory effects.<sup>16,17</sup> Moreover, one in vitro study showed PRP increases the number of rotator cuff fibroblasts, which can accelerate tendon-bone remodeling.<sup>18,19</sup> Formulations containing high concentrations of platelets can induce neoangiogenesis through VEGF and can provide a temporary matrix to aid in tissue remodeling.<sup>14</sup> However, due to the additional upregulation of matrix

metalloproteinases (MMPs), it is theorized neoangiogenesis may overall be detrimental to tendon healing.<sup>20</sup>

The beneficial effects on healing and clinical outcomes of using PRP specifically in large and massive tears have been inconsistent in higher quality clinical studies. For example, Warth et al conducted a meta-analysis of Level I and Level II studies and found that among initial tear sizes greater than 3 cm in the anterior-posterior direction, those treated with PRP had a statistically significant reduction in retear rate after double-row repair compared to controls (25.9% vs 57.1%,  $p=0.046$ ). Though there was an overall gain in Constant score when PRP was placed at the tendon–bone interface rather than over the surface of the repaired tendon ( $p=0.046$ ), it should be noted that no statistically significant differences in clinical or structural outcomes between PRP+ and PRP- groups were found for all included studies, which consisted of tears of all sizes.<sup>21</sup> Similarly, in a randomized controlled trial, Pandey et al followed 102 patients with medium (1–3 cm) and large (3–5 cm) posterosuperior rotator cuff tears who underwent single-row repair and a minimum follow up of 2 years. Large tears that were augmented with PRP at the time of repair showed statistically significant ( $p=0.035$ ) lower retear rates when compared to nonaugmented controls (4% vs 20%). They also showed that the PRP group had increased vascularity at the repair site on ultrasound at 3 months postoperatively and in the peribursal tissue, an effect which lasted at least until 12 months postop. Furthermore, the PRP group showed a significant increase in the University of California-Los Angeles (UCLA) scores at 12 months postoperatively ( $p < 0.05$ ) and Constant scores 24 months postoperatively ( $p < 0.05$ ).<sup>22</sup>

In another study, Jo et al conducted a randomized clinical trial with PRP augmentation for large and massive rotator cuff repairs. Among 48 patients at minimum of 9 months MRI follow-up, the PRP group had a retear rate of 20%, whereas the retear rate was 55.6% in the control group ( $p=0.023$ ). However, there was no significant difference in clinical outcomes between the two groups.<sup>23</sup> The authors concluded that better structural integrity in the PRP group might suggest improved clinical outcomes at longer term follow-up, but the relationship at the present time is still unknown. In a more recent randomized clinical trial by the same group that was restricted to medium to large tears (1–5 cm), the PRP treated group had a significantly lower retear rate (3.0% vs 20.0%  $p = 0.043$ ) than the control and a significantly larger increase in cross-sectional area of the supraspinatus at 1-year postop compared to preop values.

The authors concluded that PRP dramatically improved postoperative healing and attributed their good results to their leukocyte-poor formulation.<sup>24</sup> Further reasoning can be supported by basic science studies showing that high concentrations of leukocytes in PRP can cause a greater acute inflammatory response<sup>25</sup> and increased activity of matrix metalloproteinases to enhance catabolic signaling.<sup>26</sup>

On the contrary, a randomized controlled trial performed by Antuna et al showed PRP has no advantage in increasing healing in large and massive tears. Out of 28 total patients with 1-year MRI follow-up, the rate of re-tear in the PRP group was 71% whereas it was 64% in the control group, with no statistically significant differences found. Also, no significant differences were found in Constant and DASH scores at 1 year.<sup>27</sup> We believe this to be a study of lower quality because the details of their PRP formulation were not explicitly reported. The only information provided was 6 mL of PRF (Vivostat PRF<sup>®</sup>, Alleroed, Denmark) were used.

In many meta-analyses studying the efficacy of PRP in all sizes of tears, there also has been a discordance of results with no overall clinical superiority of PRP versus untreated controls.<sup>21,28–33</sup> Saltzman et al conducted a systematic review of meta-analyses and concluded that PRP used at the time of arthroscopic rotator cuff repair did not improve overall re-tear rates or outcome scores. On subgroup analysis they found significant superiority of PRP treatment in patients with small and medium-sized tears versus large and massive, in the setting of a double-row repair, and when PRP was applied at the tendon–bone interface in

solid, over liquid, formulation.<sup>34</sup> The authors noted that the results could be due to less load on the anchor points in small to medium tears compared to large and massive tears. Also, better biomechanical stability and vascularization in small to medium tears might allow for enhanced incorporation of growth factors to affect the healing process.<sup>35</sup> We believe the results of this review should be interpreted with caution. As the authors further state, there was a substantial amount of heterogeneity in terms of surgical fixation technique, performance of acromioplasty at the time of surgery, size of rotator cuff preoperatively, type of imaging used to assess re-tear occurrence, and preparation, formulation, and means of administration of PRP.<sup>34</sup>

Given the high rates of re-tear after arthroscopic repair of large and massive tears, there is an opportunity to find and utilize an effective formulation of PRP to improve healing and clinical outcomes. In studies limited to large and massive tears, some randomized controlled trials report PRP's structural healing potential. However, these RCTs lack extended follow-up. Also, as shown by the meta-analyses presented here, PRP's effectiveness is still up for debate. Thus, there is insufficient evidence to suggest a recommendation for its use. A recent 2016 AAOS consensus statement identified several obstacles to the advancement of PRP therapies and made recommendations on how future research efforts should be directed to overcome these challenges. Reasons most likely stem from a failure of many studies to include sufficient experimental detail of their PRP formulations. This has led to a wide variability of preparation protocols and formulations (Table 1), and thus the

**Table 1** Level I Studies of PRP

Study (Year) (RC Size)	Platelet Concentration	WBC Concentration	RBC Concentration	PRP Preparation Protocol
Pandey et al (2016) (med/large) <sup>22</sup>	Platelets: 474.00 $\times 10^5/\mu\text{L} \pm 0.3$	WBCs: 0.004 $\times 10^3/\mu\text{L} \pm 0.001$	RBCs: 0.000001 $\times 10^6/\mu\text{L} \pm 0.000001$	50 mL blood drawn, citrate phosphate dextrose added to blood in 7:1 ratio; stored up to a day at room temperature; 10% calcium chloride mixed in 5:1 ratio to activate PRP; applied over repair site
Jo et al <sup>23</sup> (2013) (large/massive)	Platelets: 1096.48 $\times 10^3/\mu\text{L} \pm 255.40$	WBCs: 0.04 $\times 10^3/\mu\text{L} \pm 0.06$	RBCs: 0.18 $\times 10^3/\mu\text{L} \pm 0.06$	Blood drawn 1 day prior to surgery and stored at room temperature; 0.3 mL of 10% calcium gluconate added to 3 mL of PRP; PRP placed at tendon–bone interface
Jo et al <sup>24</sup> (2015) (med/large)	Platelets: 1218.40 $\times 10^3/\mu\text{L} \pm 334.69$	WBCs: 0.04 $\times 10^3/\mu\text{L} \pm 0.03$	RBCs: 0.14 $\times 10^3/\mu\text{L} \pm 0.04$	Blood drawn 1 day prior to surgery and stored at room temperature; 0.3 mL of 10% calcium gluconate added to 3 mL of PRP; PRP placed at tendon–bone interface
Antuna et al <sup>27</sup> (large/massive)	No reference values provided			

**Abbreviations:** RC, rotator cuff; WBC, white blood cell; RBC, red blood cell; PRP, platelet-rich plasma.

inability to identify if an effective formulation exists.<sup>36,37</sup> We, therefore, suggest that future studies should focus on reporting their formulations and application processes in order to obtain a better understanding of its potential benefits.

## Scaffolds: ECM vs Synthetics

There has been an evolving role for the use of Extracellular Matrix (ECM) scaffolds and synthetic scaffolds to biologically enhance the intrinsic healing potential and mechanically reinforce surgical repair of the tendon to bone interface, respectively. ECMs are biologic scaffolds derived from fascia lata and decellularized mammalian tissues, such as dermis and small intestine submucosa, and can be classified as allografts or xenografts. Synthetic scaffolds are composed of many different types of polymers, such as polypropylene, poly-L-lactic acid, polycarbonate polyurethane, polycaprolactone, and polydioxanone.<sup>38</sup> Both types of scaffolds can be used for either augmentation (onlay) of a reparable large to massive tear<sup>39</sup> or bridging (interposition) of an irreparable tear.<sup>40</sup> Xenografts, specifically porcine small intestine submucosa, have fallen out of favor over the last decade due to 20–30% of patients in clinical trials developing a hypersensitive immune response,<sup>41,42</sup> and no significant differences found in structural failure and outcomes when used in augmented vs nonaugmented controls.<sup>43</sup>

Most recently, acellular human dermal collagen allografts, a type of extracellular matrix scaffold, have become popular for augmenting or bridging large and massive rotator cuff tears. These grafts lack cellular components, which minimize the risk of a host inflammatory response and allow for an active remodeling of organized tissue.<sup>44</sup> In a two-tendon posterolateral rotator cuff tear cadaveric study by Van der Meijden et al, the collagen scaffold augmentation was biomechanically superior to single-row repairs and equivalent to extended, linked double-row repairs.<sup>10</sup> Barber et al published one of the few Level I studies on human acellular dermal allografts and studied patients undergoing arthroscopic repair of 2 tendon rotator cuff tears greater than 3 cm. The use of acellular dermal allograft showed a retear rate in 15% of the augmented repairs vs 60% in the nonaugmented controls ( $p < 0.01$ ) on MRI at greater than 12 months follow up.<sup>45</sup> Two case-control studies also showed a statistically significant decrease in retear rates with acellular dermal allograft augmentation.<sup>46,47</sup> In revision repair of 13 shoulders with massive posterolateral tears, Petri et al found an ASES

score improvement of 21.5 points, with no patients requiring further surgery at mean 2.5-year follow-up.<sup>48</sup> In other retrospective case series on large and massive tears, failure rates for acellular dermal allografts are between 10% and 40%, with all showing improved clinical outcomes compared to preoperative evaluation.<sup>48–53</sup> Furthermore, in a systematic review of different types of scaffolds, D'Ambrosi et al found that allografts had the lowest retear rate (16.4%).<sup>54</sup>

Synthetic scaffolds are advantageous for their mechanical strength and decreased risk of disease transmission. However, they pose a higher risk of bio-incompatibility as they can induce foreign body reactions that lead to infection, decreased stability, synovitis, osteolysis, and osteoarthritis.<sup>55</sup> To date, limited human studies exist documenting the durability of synthetic scaffolds for augmentation, and most have utilized different combinations of polymers. The only comparative study to date, a 3-year cohort in massive tears, compared a polypropylene synthetic graft augmented open repair to repair augmented with a collagen patch and a repair only group. At 12 months, the retear rate was 17% for the synthetic patch, 41% for repair only, and 51% for the collagen augmented repair. At 36 months, patients treated with a polypropylene patch compared with both groups had statistically significant increases in UCLA scores, abduction strength, and elevation.<sup>56</sup> Proctor et al utilized a poly-L-lactic acid synthetic patch to treat 18 patients with large to massive rotator cuff tears. Ultrasound showed that 15 of 18 patients had intact rotator cuff repair at 12 months, and 14 intact at 42 months, with ASES scores improving from 25 preoperatively to 71 at 12 months postop ( $p=0.03$ ).<sup>57</sup>

Recent systematic reviews have looked at healing rates for various scaffolds in augmentation versus bridging repair. Steinhaus et al conducted a meta-analysis on 24 studies of large to massive tears and concluded that retear rates may be lower with the bridging technique compared to augmentation when performed in patients with ECM and synthetic scaffolds. Xenografts were the most inferior in clinical and functional outcomes and had the highest retear rates.<sup>58</sup> Ono et al conducted a systematic review in large to massive tears and found the bridging group had a 77.9% healing rate compared to 64% in the augmentation group, which was not significant. The authors concluded that inferior healing in the augmentation group might be because augmentation is not capable of altering the inherently high tension of the repair.<sup>59</sup>

One possible way to improve healing of the rotator cuff is to augment synthetic scaffolds with biological factors, such as bone marrow-derived stem cells. This combines the mechanical stability provided by synthetic polymers<sup>39</sup> and the release of chemical signals to induce tissue regeneration that are provided by stem cells.<sup>60</sup> Yokoya et al compared a polyglycolic acid (PGA) graft seeded with autologously cultured mesenchymal stem cells (MSC) with a PGA sheet alone. In the MSC group at 16 weeks, they found a higher ratio of type I to type III collagen and superior tensile strength in regenerated tendons.<sup>61</sup> This technique shows extraordinary promise given the benefits synthetic and biological components each have shown separately, and future research should focus on human studies to prove that an integrated scaffold is worthy of consideration.

Superior capsule reconstruction (SCR) is another promising direction of graft reconstruction that is being increasingly used to treat irreparable rotator cuff tears. In this technique, the graft is attached medially to the superior glenoid tubercle, instead of the tendon stump to reconstruct the superior capsule of the shoulder and prevent superior escape of the humeral head. In one of the early biomechanical studies on the technique, Mihata et al showed that SCR provided greater superior stability than the traditional methods of bridging where the graft was connected from the torn supraspinatus tendon to the greater tuberosity.<sup>62</sup> Further studies using autologous fascia lata graft of 6–8 mm thickness by the same group have shown excellent healing rates. In their first study of 23 patients, they found 83.3% of patients had no graft tears or retears of the repaired rotator cuff tendon at a mean follow up of 34.1 months. Also, ASES score improved significantly in patients with healing versus patients who had retears ( $p < 0.0001$ ).<sup>63</sup> A more recent study by the same group found healing in 95 of 100 patients, significant preop to postop improvements in mean ASES score (36 to 92), and high rates of return to sport and physical work.<sup>64</sup> Dermal allografts, which can potentially avoid donor site morbidity experienced with autologous fascia lata, have also shown promising results in the United States. Using 3 mm thick dermal allografts, Lacheta et al found a significant improvement in all clinical outcomes, with graft integrity rates of 100% (21 of 21 patients) on the tuberosity side, 76% (16 of 21 patients) at the midsubstance, and 81% (17 of 21 patients) on the glenoid side. No significant differences in clinical outcome scores ( $P > 0.930$ ) were found in patients with intact grafts versus those with torn grafts.<sup>65</sup> Denard et al

showed a 45% healing rate at 1 year postoperative MRI and 18.6% of patients underwent a revision procedure.<sup>66</sup> In 86 patients, Pennington et al used 3 mm thick grafts and reported an increase in ASES score from 52 to 82, and an increase in mean acromiohumeral distance of 7.1 mm to 9.7 mm postoperatively.<sup>67</sup> Based on the slightly inferior results reported in the US, the thickness of the graft may have a large effect on clinical outcomes and healing optimization, but its effect at this time is unknown.

It should be noted that in comparing the biochemical properties of synthetic and biologic scaffolds (Table 2), none match the native supraspinatus tendon.<sup>68</sup> Though there are issues that still remain, such as the optimal construct, the correct indication, and efficacy, both ECM and synthetic scaffolds, as well as SCR can be used, especially in situations where native tendon is compromised, and additional mechanical augmentation is needed.

## Stem Cells

In the last few years, there has been a proliferation of research concerning cell-based therapies to improve tendon healing. Bone marrow-derived stem cells (BMSCs) and adipose-derived stem cells (ADSCs) are two types of mesenchymal stem cells (MSCs) that have been the primary focus of preclinical studies. Due to their ability to

**Table 2** Summary of Scaffolds

Scaffold	Summary of Literature
<b>ECM</b>	
Xenografts	Porcine small intestine submucosa xenograft unsafe due to severe inflammatory reactions reported in high quality studies; <sup>41,42</sup> Inferior clinical and structural results reported in meta-analyses <sup>58,59</sup>
Acellular Human Dermal Allograft	Significantly improves retear rates and improves outcomes scores in high level studies when used for augmentation of large and massive tears <sup>45–48</sup>
<b>Synthetics</b>	
Polypropylene	Significantly improves retear rates compared to repair alone <sup>56</sup>
Poly-L-lactic acid	High healing rates and significantly improves outcomes <sup>57</sup>
Healing rates for augmentation vs bridging repair; <sup>a</sup> Bridging > Augmentation	

**Notes:** <sup>a</sup>as reported in the meta-analyses of mostly Level III and IV studies by Steinhaus et al and Ono et al.

become tenocytes, chondrocytes, osteoblasts, and produce growth factors, MSCs have the potential to increase the regeneration of the enthesis and improve the strength and quality of the repair.<sup>69</sup> The repair of massive tears in particular is usually compromised by chronic lesions with advanced fatty degeneration and atrophy and it is in this realm that MSCs have shown the greatest healing potential. Sevivas et al injected MSC secretomes (paracrine factors) into a rodent model with induced 2-tendon massive rotator cuff tears and found that MSCs showed a reduction of muscle fatty degeneration and atrophy, with more reproducible results in single local injection compared to multiple systemic injections.<sup>70</sup> Similar results were replicated with ADSCs in rodent models with simulated chronic subscapularis tears<sup>71</sup> and chronic massive tears.<sup>72</sup> While these studies show that stem cells could possibly be effective in augmenting repair, they also indicate promise as a conservative treatment.

Additional literature on the histology and biomechanics of BMSCs and ADSCs have been studied in animal models with success,<sup>73–76</sup> but human studies thus far have been limited, especially in large and massive tears. In a human study with the longest follow-up in the literature, Hernigou et al evaluated 10-year results of 90 patients who underwent single-row repair augmented with BMSCs vs a matched control group without augmentation. At 10 years, 87% of patients in the BMSC group had intact rotator cuffs compared to 44% in the control group;<sup>77</sup> however, this study only looked at rotator cuff tears of 1.5 to 2.5 cm. No human trials utilizing ADSC augmented full-thickness repairs exist, but the first human study using ADSCs alone, a dose-escalation trial for the treatment of partial-thickness tears, showed that the volume of articular and bursal side defects decreased by 83% and 90% in the mid and high dose groups, respectively.<sup>78</sup> To our knowledge, no human studies on the effect of BMSCs and ADSCs involving large and massive tears have been published.

A new source of mesenchymal stem cells, those obtained from the subacromial bursae, are now also a subject of interest. In one study, these cells demonstrated strong chondrogenic, adipogenic, and osteogenic potential similar to BMSCs as evidenced by histological, immunohistochemical and PCR analyses.<sup>79</sup> When pretreated with bone morphogenetic protein-12 (BMP-12), bursal cells expressed markers of tenocytes, and when seeded in ceramic scaffolds, they formed extensive bone and tendon-like tissue.<sup>80</sup> Although the subacromial bursa is typically identified as a source of pain and discarded as medical waste

during arthroscopic surgery, early studies show promise for its ability to improve the healing potential of rotator cuff tears.<sup>81</sup>

If MSCs are applied to augment the repair of large and massive tears, healing efficacy will likely depend on the chronicity, ie fatty degeneration and muscle atrophy, and size of the defect. Equally important to their efficacy will be the way in which MSCs are harvested, processed, and prepared. According to the International Society for Cellular Therapy statement in 2006, researchers use different methods of isolation and expansion of MSCs, and different approaches to characterizing the cells, making it difficult to compare and contrast study outcomes. Standardized reporting measures would thus decrease the regulatory ambiguity and hopefully expand the conditions for use.<sup>82</sup> As it currently stands, BMSCs and ADSCs are low-risk and not subject to strict regulation by the FDA if they undergo minimal manipulation, are for homologous use only, are not combined with a drug or device, and are autologous or used in a first-degree or second-degree blood relative.

## Conclusions

PRP, scaffolds, and stem cells can potentially improve clinical outcomes by enhancing the healing environment after repair of large and massive tears. PRP has been the most studied and shows decreased retear rates compared to controls in some high-quality studies. However, whether there is any difference in outcomes between repairs augmented with PRP vs no augmentation remains to be determined. We believe that the inconsistencies in results are due to the variability in PRP preparation and administration used across studies. For scaffolds, evidence has become clearer on the inferiority of existing porcine small intestine submucosa xenografts due to their hypersensitive immune responses and equivalent outcomes and healing rates to repair alone. ECMs, specifically acellular human dermal allografts, can decrease retear rates and improve clinical outcomes when used to augment or bridge repairs of large and massive rotator cuff tears. Synthetic scaffolds have been much less studied, but in retrospective studies, their increase in healing and short-term outcomes can be attributed to their durability. A future area of scaffold research concerns a combination, ie a scaffold coated with MSCs, which may prove useful in human therapies. Cellular augmentation with MSCs alone could prove to be therapeutic due to the secretion of numerous growth factors,

**Table 3** Author Grades of Recommendation for Biologics

	PRP	Dermal Allograft Scaffold	Synthetic Scaffold	Xenograft Scaffold	Superior Capsule Reconstruction	Mesenchymal Stem Cells
Large and Massive Rotator Cuff Repair	Grade C	Grade B	Grade I	Not recommended	Grade C	Grade I

**Notes:** 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.

**Abbreviation:** PRP, platelet-rich plasma.

cytokines, and vesicles conducive to healing, but human studies are lacking and the clinical benefit is unknown.

In summary, patients with large and massive rotator cuff tears have great potential to benefit from biologics if an optimal formula is found. Future prospective high-quality studies are needed in order to better define the role of the biologics mentioned in this article. Perhaps a combination of scaffold, PRP, and stem cells, used temporally during the treatment process could provide the greatest improvement in healing and outcomes. Until additional studies are published, we recommend the following based on the given data (Table 3). Due to mixed results in RCTs and meta-analyses, usage of PRP as an adjunct to rotator cuff repair in this patient population cannot be recommended at this time. Acellular dermal allografts are preferred over synthetic scaffolds due to a greater amount of published human studies. They should be used in situations where native tendon is compromised and additional mechanical augmentation is needed. Early studies from SCR report a wide range of healing rates (45–95%),<sup>63–66</sup> despite increases in clinical outcomes. Stem cells have been the least studied to date and there is insufficient evidence to give a recommendation for their use at this time.

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Disclosures for Dr. Peter J. Millett, MD, MSc

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