Ortho-Biologics for Ligament Repair and Reconstruction

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KEYWORDS

- Platelet-rich plasma • Anterior cruciate ligament • Growth factor
- Transforming growth factor • Bone marrow aspirate concentrate

KEY POINTS

- Despite the recent appraisal of biologics within treatment protocols, no clear algorithm for indication, processing methodology, or application exists currently.
- There is a significant potential for enhancement of tissue healing within both acute and chronic conditions in restoring native or near native tissue.
- Biologics may provide an alternative to surgical intervention when nonoperative treatment is preferred by patients or surgeons.
- When biologics are used in addition to surgical intervention, there is a potential for enhanced bone mineral density, bone volume, overall graft integrity, and vascularity within cells.
- Currently, the literature is inconsistent in providing definite conclusions on outcomes and usage of biologics for the treatment of musculoskeletal injuries; but laboratory, animal, and some clinical studies have provided promising results for the future direction of ortho-pedic treatment protocols and rehabilitation.

INTRODUCTION

Novelties and technology improvement for ortho-biological therapies, tissue grafting, and surgical augmentation have exhibited overwhelming growth in the past decade.[1] At first, biologics were envisioned to enhance tissue healing in both acute and chronic conditions by stimulating the recovery processes to restore native or near-native tissue while reducing risks for treatment failure. Nonetheless, symptom

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management has recently become another important indication for their use.[2–4] The most popular biological modalities currently used for the treatment of acute and chronic musculoskeletal conditions and as adjuvants for conservative and surgical approaches include hyaluronic acid, single/combined growth factors (GFs) therapy, platelet-rich plasma (PRP) (Figs. 1 and 2), and bone marrow aspirate concentrate (BMAC) (Fig. 3).

However, despite the upsurge on the use and reported success of many of these therapies, there is no clear algorithm for the indications, processing methodology, application, and reporting that has led to inconsistencies in clinical and basic science results.[5–7] Hence, establishing an optimal protocol for the treatment of various musculoskeletal entities remains a challenge because the specific treatment or combination of them, the number of applications, the processing method, and the real and long-term efficacy of these biological approaches has yet to be determined.[8,9]

Complex biomechanics, different vectors of load, and an intra-articular hostile environment have also been reported as serious obstacles to successfully adhere tissue-engineered and autologous biologics to damaged tissue, regenerate homogeneous tissue, and finally revascularize the tissue sufficiently and timely to prevent a future reinjury.[10–12] For the aforementioned reasons, the purpose of this article is to review current concepts on several biological treatment approaches as an adjuvant for the most commonly performed ligament injuries repair or reconstructions.

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Anterior Cruciate Ligament

Despite being one of the most frequent procedures in orthopedics (reported to be the sixth most common),[13] limited progress has been made to improve anterior cruciate ligament (ACL) reconstruction and its healing capacity or to improve the time of ACL graft ligament incorporation to enhance knee biomechanics, reduce the return to sports times, and ultimately limit the development of degenerative joint changes.[14–17]

In this regard, regenerative treatment protocols are thought to have the potential to improve current surgical ACL interventions by enhancing graft incorporation and
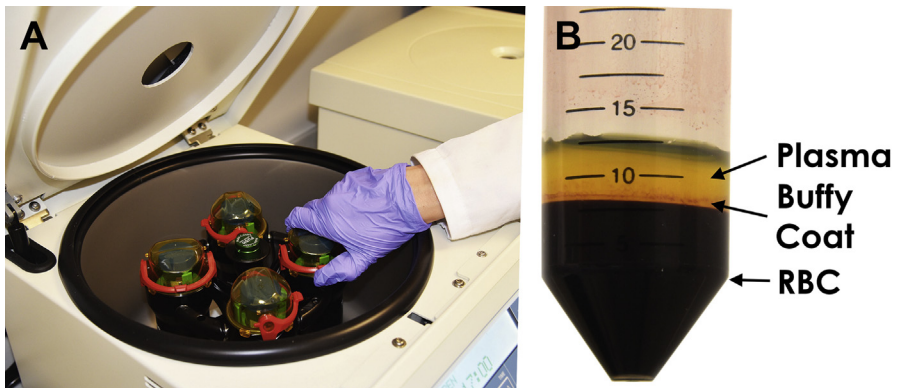
**Fig. 1.** (*A*) The centrifuge setup for processing of PRP and (*B*) the final result with 3 distinct layers of cellular material after processing the sample. At the top of the test tube is the platelet-poor plasma; beneath this layer is the buffy coat where most platelets lie (the deepest layer of the buffy coat layer contains high concentrations of white blood cells), and at the bottom layer are the red blood cells (RBCs).

Fig. 2. A double syringe system for injection (11:1 ratio allowing homologous mixture of the PRP [*left*] and a gelling agent solution [*right*], respectively). Gelling agent solution typically consists of thrombin and 10% calcium chloride (CaCl) solution (1000 IUs thrombin:1 mL CaCl). LR, leukocyte rich.

strength, gene activation, trophic induction, and microenvironment facilitation and signaling with cells or bioactive factors to optimize, delay, or prevent premature progression of osteoarthritis.[18] It is accepted that the success of an ACL reconstruction depends heavily on biological processes for each phase of the healing process. Commonly reported regenerative modalities contain various GFs, including transforming GF β-1 (TGF-β1), fibroblast GF-2 (FGF-2), insulinlike GF, epidermal GF, platelet-derived GF (PDGF), and vascular endothelial GF (VEGF). These GFs have demonstrated positive effects on cell proliferation, cell migration, angiogenesis, and extracellular matrix (ECM) production in numerous cell types of both in vivo and in vitro models.[19]

The primary cell in the ACL is the fibroblast. The fibroblast has receptors for many of these GFs, including PDGF, TGF-β, and FGF. For example, PDGF stimulates fibroblast growth, migration, and biosynthetic activity,[20] which could promote an improved ligamentization of the graft used for ACL repair or reconstruction and minimize the proinflammatory factors released immediately after surgery but might also contribute to a better and faster integration of the graft within the femoral and tibial tunnels, thus, avoiding an increased failure risk.[21]
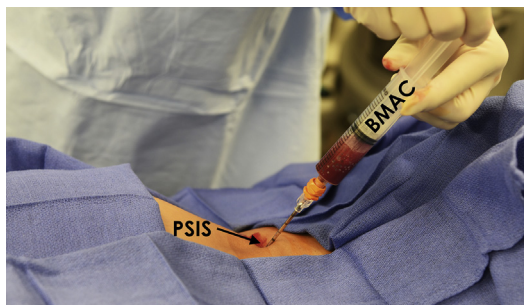
Fig. 3. A patient in ventral decubitus for BMAC from the left posterior superior iliac spine (PSIS).

Preclinical studies

Important basic science studies have been performed in the area of ligament healing in an attempt to regenerate/repair ligaments in a less invasive approach using the tissue remnants available. Although in clinical practice this is not often possible, because of the lack of viable tissue pending the severity and/or chronicity of the injury, growing preclinical work has provided the basis to improve these biological approaches. GFs, such as TGF-β1,[22] FGF-2,[23] and basic-FGF,[24] have been reported to regulate and improve cellular activities and proliferation and ECM deposition and to influence the differentiation of mesenchymal stem cells (MSCs) into fibroblasts in the repair process of torn ligaments. Particularly, the GFs outlined later have exhibited positive effects on various biological processes needed to improve ACL healing.

The TGF-β family is a key regulator during embryologic development and also plays a significant role in the early modulation of scar tissue formation during connective tissue healing.[25] Studies comparing the application of different GFs in animals with partial ACL tears and ACL explant models suggested that TGF-β1 might stimulate initial healing and overall healing both histologically and biomechanically.[26,27] Kondo and colleagues[26] reported on the effect of TGF- β1 in a rabbit ACL injury model and reported significant improvement of the biomechanical and histologic healing properties of injured ACLs treated with TGF-β1 when compared with controls. Recently, it has been reported that blocking VEGF reduces angiogenesis, graft maturation, and biomechanical strength following an ACL reconstruction in a rat model.[28] Further, a different group studied 18 sheep undergoing ACL reconstruction with either a VEGF-augmented graft or a control group. The VEGF group demonstrated improved vascularization and fibroblast infiltration; however, increased graft laxity was found at 12 weeks.[29]

Murray and colleagues[30] reported on a porcine ACL repair model using clotted PRP, suggesting that there was no beneficial effect of adding PRP when compared with controls. It was theorized that the fibrin clot containing the platelets may have been prematurely dissolved in the intra-articular environment by circulating plasmin in the synovial fluid.

These findings directed the attention to developing scaffolds to protect the graft from early degradation due to the hostile intra-articular environment. Consequently, Cheng and colleagues[31] showed that the addition of PRP to a collagen hydrogel resulted in a significantly increased cellular metabolic activity, reduced apoptotic rate, and stimulation of collagen production in the cells from the immature and adolescent animals but had less effect on adult cells animals.

A study using a rat model compared ACL regeneration between animal groups subjected to intra-articular injection of fresh whole bone marrow cells (BMCs), cultured MSCs, or saline in partial ACL tears.[32] The investigators suggested that intra-articular bone marrow transplantation using fresh whole BMCs is an effective treatment of ACL partial rupture and reported nearly normal strength and ligament healing compared with control subjects. Similarly, Kanaya and colleagues[33] reported that intra-articular injection of MSCs resulted in a healed ligament with superior histologic scores and a greater failure load compared with nontreated control knees. A recent study by Lui and colleagues[34] compared ACL reconstructions with tendon-derived stem cell sheets (after treatment with connective tissue GF) and a control group in 97 rats. The treatment arm exhibited higher tunnel bone mineral density and bone volume, better graft osteointegration, and higher intra-articular graft integrity with lower cellularity, vascularity, and cell alignment compared with the control group.

Clinical studies

Improvements in tissue engineering and regenerative medicine technology have resulted in a new interest in the biological augmentation of ACL repairs and reconstructions, including GF, PRP, stem cells, and bio-scaffolds. A recent systematic review[35] reported on 23 studies, including one reporting on stem cells, one on concomitant application of PRP and stem cells, and 21 articles on PRP. Two studies reported on ACL repair with biologics and the remaining 21 on ACL reconstruction augmented with PRP. The investigators concluded that the role of PRP on ACL repair/reconstruction is still controversial and is only related to improved graft maturation over time, without beneficial effects in terms of clinical outcome, bone-graft integration, and prevention of bony tunnel enlargement in the short-term outcome.

Seijas and colleagues[36] reported on 19 professional soccer players with partial ACL tears treated with intraligamentous placement of PDGFs into the intact bundle. Eighteen of 19 players were able to return to their previous level of play at a mean of 16.20 weeks. Platelet-rich GF (PRGF-Endoret)[37] was applied in the intact posterolateral bundle intra-articularly in a different study by Anitua and colleagues.[37] No complications and satisfactory objective results (KT-1000; MEDMETRIC, San Diego, CA) were reported in this study, and postoperative MRI evaluation demonstrated complete ligamentization at 1 year after surgery with good anatomic arrangement.

Radice and colleagues[38] reported on 100 ACL reconstructions prospectively, comparing PRP gel (PRPG) with a control group. Notably, graft homogeneity was 48% shorter in the PRPG group (179 vs 369 days). Additionally, Vogrin and colleagues[39] reported on 50 patients (25 thrombin-activated PRP-soaked grafts and 25 control group) and demonstrated improved anterior-posterior instrumented knee stability via a KT-2000 (MEDMETRIC; San Diego, CA) arthrometer at 6 months. Conversely, Nin and colleagues[40] reported on 100 patients undergoing an ACL reconstruction with bone-tendon-bone allograft (double-blind randomized clinical trial). The investigators reported no difference was found in terms of subjective outcome, biomechanical integration, or graft integration at 2 years' follow-up.

Gobbi and colleagues[41] evaluated the 5-year clinical results of PRP injection in 58 athletes treated by ACL suture repair in addition to microfracture of the intercondylar notch. They reported that 78% of the patients returned to their sports activities. The side-to-side difference in anterior translation significantly decreased from 4.1 mm (SD = 1.6) preoperatively to 1.4 mm (SD = 0.8) postoperatively (P <.05). Four patients had a retear during sporting activity and underwent an ACL reconstruction within 2 years from the primary repair surgery. This case series concluded that PRP injection was effective in restoring knee stability and function in young individuals with acute partial ACL tears.

Limited evidence exists on histologic data for PRP application after ACL reconstruction. Sanchez and colleagues[42] compared PRGF-assisted ACL reconstructions versus nonaugmented ACL reconstructions that required a second-look arthroscopy (loose body or hardware removal, meniscal tears treatment, or cyclops lesions resection) at a minimum of 6 months. Although gross morphology demonstrated no difference, histologically, newly formed connective tissue enveloping the graft was found in 77.3% of the intervention group versus 40.0% of control subjects.

Concerning BMAC application as an adjuvant for ACL surgery, Centeno and colleagues[43] reported on 10 patients with ACL tears treated with an intraligamentous injection of autologous bone marrow concentrate and PRP using fluoroscopic guidance. ACL laxity and MRI evidence of a grade I, II (partial), or III (complete) tears were documented (always with <1 cm retraction of the ACL stump). ACL tears were assessed by MRI, and software was used to objectively quantify changes of ligament integrity

through 5 different types of measurements of ACL pixel intensity. Seven of 10 patients showed improvement in at least 4 of these 5 objective MRI measures. The mean visual analog scale change decreased by 1.7 (P = .25), and the mean Lower Extremity Functional Scale increased by 23.3 (P = .03); a mean improvement of 86.7% was reported.

Medial Collateral Ligament

Isolated medial collateral ligament (MCL) injuries are the most common knee ligament injuries and are typically managed with conservative treatment resulting in satisfactory results. However, mechanical and histologic properties typically do not return to normal.[44,45] For this reason, the use of PRP to advance MCL healing has been proposed.[46]

Preclinical studies

Despite the frequent use of PRP to treat ligamentous injuries, there is limited information on the use of PRP in basic science; clinical trials to determine if improvement can be achieved for biomechanics or ligamentous healing can be accelerated.[47] LaPrade and colleagues[48] reported that one single dose of either PPP or a 2-times dose of PRP at the time of injury did not accelerate ligament healing (**Fig. 4**). Additionally, a 4-times dose of PRP demonstrated a significant negative effect on ligament strength and collagen orientation (relative to the sham group) at 6 weeks after injury. The investigators concluded that MCL tears treated with PRP immediately after injury or surgery may not improve healing at low doses of PRP and could be harming ligament healing at higher PRP doses. In a biomechanical analysis, Yoshioka and colleagues[49] reported significantly improved structural properties of MCLs in rabbits treated with leukocyte-reduced PRP relative to controls. However, no analysis was performed taking the native ligament biomechanical properties; only a comparison between the PRGF and untreated group was made.

Clinical studies

Literature on the beneficial effect of PRP treatment of MCL injuries is limited. Only one level IV case study report has evaluated the clinical use of PRP with outcomes of isolated grade II MCL injuries.[50] Eirale and colleagues[50] described a successful case of a competitive soccer player in which they opted for conservative treatment with multiple PRP injections and rehabilitation. The athlete returned to play after 18 days with excellent functional scores and without symptoms, but radiological imaging showed
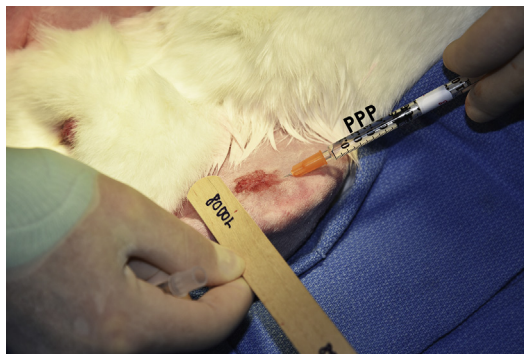
Fig. 4. A rabbit MCL being injected with PPP after creating a grade III tear to the ligament to determine the effect of different concentrations of platelets in MCL healing.

incomplete healing of the ligament.[50] Despite this, the athlete had no recurrence of injury or further complications at 16 months' follow-up.[50] This study gives evidence that PRP may play a role in MCL healing with conservative treatment; however, it is encouraged that further clinical outcome studies be performed to elucidate the value of PRP with MCL injury.

Ulnar Collateral Ligament of the Elbow

Enhancing the treatment options for ulnar collateral ligament (UCL) deficiency has long been of interest in the world of sports medicine. Highly prevalent among overhead-throwing athletes, primarily with baseball pitchers from youth to professional levels, improved UCL reconstruction techniques have resulted in increased return-to-play rates between 53% and 90% after once being thought of as a career-ending injury.[51–56] However, there is a disparity in the literature on the postoperative UCL reconstruction outcomes because it has been reported that 3% to 40% of surgical reconstructions result in complications.[57–60] Although there is a multitude of factors that influence UCL recovery, adjunctive treatments like PRP and MSCs may accelerate the timetable for athletes returning to sport and improve overall outcomes. Additionally, biological injections could possibly serve as a nonoperative treatment, acting to bypass a year-long recovery period and pose as an alternative to the perceptually adhered to Tommy John surgery.[56,61,62]

Preclinical studies

To the authors' knowledge, no preclinical studies have been performed specifically evaluating the use of biologics for UCL healing. Because of the potential therapeutic use that has been seen for ACL, rotator cuff, and Achilles tendon injury in animal models, it is thought that PRP and MSCs can be applied to UCL injury and are frequently used in clinical settings.

Clinical studies

Two studies have used biological adjuncts for nonoperative treatment of a partial UCL tear with promising results, in contrast to clinical outcomes seen in other joints.[59,63] In a case series of overhead-throwing athletes, Podesta and colleagues[63] reported that 88% of athletes with partial UCL tears returned to normal levels of play at 12 weeks after a single PRP injection. Along with satisfying functionality, the investigators also reported decreased medial elbow joint space on valgus loading.[63] Furthermore, another study of 44 competitive baseball players reported that 73% of athletes had good to excellent results following a PRP injection when supplemented with a return-to-play rehabilitation program.[59] Unfortunately, no clinical studies of conservative management of complete UCL injuries with MSCs or scaffolds have been published.[62] However, with the increasing popularity of these methods for treatment of shoulder and knee joint injuries, it should be expected that MSCs and scaffolds would serve a significant role in future UCL treatment techniques.

SUMMARY OF RECOMMENDATIONS

In recent literature, biologics have been shown to have positive results in improving tissue regeneration in laboratory and animal studies; but in the clinical setting, results are mixed in demonstrating its efficacy for patient care. The use of PRP has been tested in both forms of rehabilitation following surgery as well as a replacement to ligamentous reconstructions for patients/surgeons wishing to avoid surgical intervention, but outcomes are clouded among beneficial and neutral effects. With more consistent results of MSC and PRP effects on patient outcomes (preferably with objective data,

such as imaging or histology), the future direction of orthopedic treatment may continue to progress further into less invasive procedures.

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