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Advances and Future Directions and Technologies in Orthobiologics

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Orthobiologics are a diverse class of biologically-derived materials utilized in the treatment of a wide range of musculoskeletal pathologies. Within sports medicine, these materials are becoming more frequently used both in clinical settings and in the operating room. Commonly included treatments include platelet rich plasma (PRP), concentrated bone marrow aspirate (cBMA), adipose-tissue derived therapy, and perinatal derived therapy. These materials promote tissue healing and regeneration through a variety of cellular mechanisms. Several emerging approaches for orthobiologic delivery and application, such as exosomes, induced pluripotent stem cells, and injectable cytokines and peptides, have also demonstrated promise. The efficacy of orthobiologics is heavily condition-dependent, with good evidence for substantial outcomes in some pathologies and limited effects in others. Current challenges within orthobiologics include a lack of standardized preparation, dosing, formulation, and nomenclature within the field. This is further complicated by a dynamic regulatory landscape. The future of orthobiologics will likely focus on standardizing research trials and data collection. More research is needed to firmly establish the uses, side effects, cost-effectiveness, and long-term outcomes of orthobiologics.
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Introduction

Orthobiologic agents are a broad and diverse class of treatments derived from biological sources that are utilized to positively affect musculoskeletal tissue healing.[1–3] These agents are currently under investigation or used clinically for the treatment of a wide range of musculoskeletal pathologies.[1,4,5] The current application of orthobiologic treatments is for the nonoperative treatment of musculoskeletal pathologies and the augmentation of surgical treatment by addressing biologic deficiencies at the cellular or molecular level in the respective disease or tissue healing process. Presently, orthobiologic agents are classified as being 'symptom-modifying' rather than 'structure-modifying' treatments, as they may improve function or reduce pain, but a lack of evidence exists to prove they regenerate tissue in humans.[6]

Academic interest and utilization of orthobiologics have grown substantially in recent years. In orthopaedic sports medicine, a survey by Noback et al. reported that 66% of respondents from the American Orthopaedic Society for Sports Medicine (AOSSM) utilized orthobiologics, with the majority indicating an intention to further increase their use.[5] Similarly, a systematic review of literature conducted by Obana et al. demonstrated a rising trend in publications related to well-established orthobiologic treatments across several major orthopaedic journals over 11 years beginning in 2009.[7] Despite this enthusiasm, numerous challenges currently exist in the investigation and clinical application for orthobiologic treatments. Commonly identified challenges to the application of orthobiologic treatments include the inconsistent use of terminology and use of misleading

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nomenclature, inconsistencies in the techniques reported in existing basic science and translational research studies that create difficulty in the understanding of clinical outcomes, wide variabilities in the composition and biologic properties of orthobiologic agents, and a limited understanding of how to best match the appropriate orthobiologic agent with the specific tissue or pathology being treated.[8,9] Furthermore, existential barriers to the use of orthobiologic agents are present, specifically with regard to regulatory processes and the cost of use, as many orthobiologic treatments are not covered by commercial insurance.[10]

This review article seeks to provide a summary review of currently available and commonly utilized orthobiologic treatments. Additionally, a description of clinical recommendations for these agents based on existing and emerging evidence is also provided. Future directions and technologies in orthobiologics are also provided, given the evolving status of these therapies.

Autologous Blood-Derived Formulations

Platelet Rich Plasma

Platelet-rich plasma (PRP) is an autologous plasma derivative containing approximately 3-5 times the number of platelets and growth factors as found normally in blood.[1,3] PRP is prepared by centrifuging peripherally drawn blood from a patient to isolate its components by density (Figure 1). After isolation, the PRP layer is then injected back into the target area of the patient to treat a variety of joint or soft tissue pathologies. Basic science and translational research support the effects of the use of PRP, as the platelets administered contain a wide variety of cytokines and bioactive molecules that mediate soft tissue healing cell proliferation, chemotaxis, cell differentiation, and angiogenesis.[3]

Significant heterogeneity exists in the characterization of PRP composition, which may also vary widely depending upon numerous factors involved in its preparation, including patient age, sex, health status, time of day of acquisition, proprietary system or centrifuge used in the preparation, centrifuge setting and time, and the use of anticoagulants and activators.[12] Notably, the interpretation of clinical data on the efficacy of PRP is significantly limited due to the heterogeneity in its preparation, as this has the potential to significantly impact the biological activity of the PRP. There is a need to further characterize the preparation of PRP for accurate scientific communication, as well as to better understand its clinical application. PRP formulations are commonly classified as either 'leukocyte-rich' or 'leukocyte-poor,' although more granular classifications based on platelet count, leukocyte subtype composition, and individual growth factor or signaling molecule concentration may be necessary, as these may also be important determinants of biological efficacy *in vitro*.[13] While this biological activity may be symptom-modifying, current evidence does not support that the

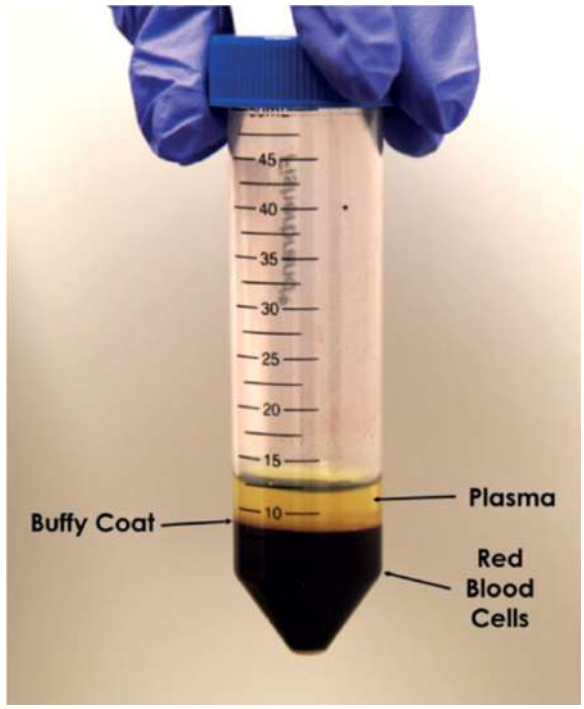

Figure 1 Preparation of PRP. Following 1 to 2 spin cycles, 3 distinct layers are visible: red blood cells at the bottom, the buffy coat (containing white blood cells and platelets) in the middle, and plasma on top. The buffy coat is typically removed with a pipette to isolate the platelet-rich plasma.[11] Adapted from Moatshe G, Morris ER, Cinque ME, et al. Biological treatment of the knee with platelet-rich plasma or bone marrow aspirate concentrates: A review of the current status. *Acta Orthop*. 2017;88(6):670–674. https://doi.org/10.1080/17453674.2017.1361962. Licensed under CC BY-NC 3.0.

administration of PRP is structure-modifying or affects tissue regeneration.[14]

Common applications include the treatment of osteoarthritis, various overuse tendinopathies, ligamentous injuries, and as a surgical augment for repair or reconstruction of soft tissue structures.[14] At present, mixed clinical data exists regarding the efficacy of PRP for the nonoperative treatment of osteoarthritis or soft tissue pathologies and the augmentation of surgical procedures, though some level I evidence studies support the clinical efficacy of PRP for various pathologies. In a meta-analysis of 13 RCTs evaluating PRP versus corticosteroid injection for the nonoperative treatment of rotator cuff disease, Pang et al. reported superior functional outcomes with PRP at time points greater than 2 months postinjection and lower rates of subsequent injections or surgical intervention by 1-year postinjection.[15] Peerbrooms et al. and Mishra et al. reported significant improvement in pain and function in randomized-controlled trials (RCT) comparing the treatment of chronic lateral epicondylitis with leukocyte-rich PRP (LR-PRP) compared to control groups.[16,17] In a systematic review and meta-analysis of RCTs comparing PRP and corticosteroid injections for the treatment of lateral epicondylitis, Xu et al. reported improved pain and function at follow-up greater than 6 months postinjection.[18] In an RCT comparing ultrasound-guided dry needling with versus without LR-PRP augmentation for the

treatment of chronic patellar tendinopathy, Dragoo et al. found significant improvement in patient-reported outcomes (PROs) at 12 weeks, but no difference at longer-term follow-up.[19] Another RCT comparing LR-PRP, leukocyte-poor PRP (LP-PRP), and saline for the treatment of patellar tendinopathy found that PRP was no more efficacious than saline.[20] De Vos et al. and de Jonge et al. also reported a similar lack of radiographic or clinical improvement in RCTs evaluating the use of PRP for the treatment of Achilles tendinopathy.[21–23] With grade 2 hamstring muscle injuries, PRP was demonstrated to result in a shorter time to return to play in an RCT comparing LR-PRP to rehab alone.[24] With regard to the treatment of knee osteoarthritis, Campbell et al. reported significant improvements in pain and function up to 1-year with PRP versus control treatment.[25] Notably, the authors found that patients with less radiographic burden of osteoarthritis may benefit more from PRP than those with more severe disease. Riboh et al. also found that LP-PRP resulted in significantly greater improvement in PROs than hyaluronic acid and placebo for the treatment of knee osteoarthritis.[26]

With regard to the use of PRP as a surgical augment, Saltzman et al. found that PRP did not significantly improve retear rates or PROs for the augmentation of rotator cuff tear, though a trend existed toward some clinical benefit existing in certain repair settings, such as smaller rotator cuff tear sizes.[27] For the augmentation of anterior cruciate ligament reconstruction (ACL-R), PRP has been found to show some beneficial radiographic outcomes (graft maturation, graft-to-bone tunnel healing), however, it has not been reliably demonstrated to significantly improve clinical or functional outcomes.[28] Conflicting evidence exists regarding the efficacy of PRP for augmentation of meniscus repair. In an RCT comparing PRP versus saline for augmentation of bucket handle meniscus tears, Kaminski et al. reported significant improvements in PROs and healing rates with PRP augmentation.[29] However in separate systematic reviews and meta-analyses evaluating the efficacy of PRP on meniscus repair, Sochadki et al. reported improved healing rates and no significant difference in PROs,[30] Xie et al. reported improvement in and no difference in healing rates,[31] and Migliorini et al. reported no improvement in either outcome with PRP augmentation.[32]

Clinical outcomes evaluating the efficacy of PRP are largely limited by methodologic heterogeneity and lack of longer-term follow-up, though level I clinical data provides support for the use of PRP in the treatment of early osteoarthritis and certain soft tissue pathologies. Despite this, the current American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guidelines provide limited support for the routine use of PRP in treating various orthopaedic conditions, though recommendations may continue to evolve with emerging literature.[6]

Autologous Conditioned Serum (ACS)

Autologous Conditioned Serum (ACS) is another orthobiologic therapy with mechanistic parallels to PRP. ACS is obtained by incubating whole blood with glass beads to stimulate leukocyte activation. This process leads to the production of enriched anti-inflammatory cytokines, notably interleukin-1 receptor antagonist (IL-1Ra).[33] Given the central role of interleukin-1 receptor (IL-1R) in the pathogenesis of osteoarthritis and other arthritic conditions, IL-1Ra is hypothesized to attenuate the inflammatory cascade and exert symptom-modifying effects.[34]

Despite promising early data, the clinical application of ACS remains limited, as ACS is not licensed for general clinical use by the US Food and Drug Administration (FDA).[35] In countries where regulatory approval has been granted, ACS serum has been suggested to be more effective than PRP as it relates to functional outcomes and pain relief in osteoarthritis.[36] Jeyaraman et al., studying the use of intratendinous ACS injections on lateral epicondylitis., have also reported a significant improvement in clinical outcomes at both 3-month and 12-month follow-up.[37]

Despite some promising results at short-term follow-up, definitive conclusions from studies remain elusive due to the limited number of adequately powered and high-quality randomized controlled trials, as well as the paucity of long-term data. Further large-scale, methodologically rigorous studies are warranted to establish the clinical efficacy, optimal indications, and formulation parameters for ACS.

Bone Marrow Aspirate and Adipose Tissue

Autologous therapies derived from bone marrow and adipose tissue are currently in clinical use. These therapies require differentiation from 'stem cells,' and may be more appropriately termed connective tissue progenitor (CTP) products.[38] Stem cells are defined by 2 key characteristics: the capacity for self-renewal while maintaining an undifferentiated state, and the ability to differentiate into specialized cell types.[33] Mesenchymal stromal cells (MSCs) are purported to be a type of multipotent stem cell capable of differentiating into osteoblasts, chondrocytes, or adipocytes.[34] MSCs can be harvested from bone marrow and adipose tissue.[39] However, multiple investigations have demonstrated that truly multipotent cells are only present in minute concentrations (0.001% to 0.01%) within these cell therapy formulations.[40] Thus, the purported effects of these cell therapy formulations are likely not due to the presence of multipotent cells, but rather the high concentration of growth factors and anti-inflammatory cytokines.[41]

Formulations from bone marrow aspirate [bone marrow aspirate concentrate (cBMA)] and adipose tissue [microfragmented fat (ex. lipogems)] contain autologous, uncharacterized, nonculture expanded, and minimally manipulated cells.[38] This 'minimal manipulation' and lack of 'alteration' of the biological characteristics of the cells or tissue allows these therapies to meet Section 361 criteria under the Code of Federal Regulations Title 21, Part 1271-Human Cells, Tissue, and Cellular and Tissue-Based Products (HCT/P) and not require an independent FDA and biologic license application

approval for use.[42] This represents an important distinction from the therapeutic use of isolated and expanded MSCs, which are regulated under Section 351 and may currently only be used in a clinical trial under an Investigational New Drug (IND) application.

Bone Marrow

Bone marrow aspirate concentrate (cBMA) is a therapy created from bone marrow aspirate that is concentrated by centrifugation to isolate multiple types of cells and biological factors.[43] (Fig. 2) Analysis of cBMA has demonstrated it to contain various hematopoietic and inflammatory cells (lymphocytes, monocytes, neutrophils, platelets), MSCs, growth factors and cytokines [Platelet derived growth factor (PDGF), TGF-B, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin-like growth factor-I (IGF-I), granulocyte-macrophage colony stimulating factor (GMCSF), bone morphogenetic protein (BMP-2 and 7), and interleukins (IL-1B, 6, 8).[44–46] Despite containing minute quantities of MSCs, cBMA has not been demonstrated to result in true therapeutic tissue regeneration outside of the possible findings of its use to augment tissue to bone healing following rotator cuff repair and possibly, ACL reconstruction. That being said, it remains unclear as to the impact of the cells themselves for these findings. Therefore, like PRP, it should generally be considered symptom-modifying, rather than structure-modifying. The therapeutic effect of cBMA is considered to result from its concentration of anti-inflammatory properties and from a paracrine effect, by which its biological factors stimulate a cellular response that promotes tissue healing.[46,47]

Like PRP, these CTP products are being used for nonoperative treatment of musculoskeletal pathology and to augment several orthopaedic procedures. Emerging literature continues to evaluate their efficacy in clinical applications, and current clinical evidence remains mixed regarding their therapeutic benefit. With regard to the use of cBMA for the treatment of knee osteoarthritis, Han et al. performed a systematic review of available randomized controlled trials in 2024.[48] The authors concluded that while cBMA did show efficacy in improving pain and function at short-term follow-up, it did not demonstrate clinically significant differences from other injection modalities. cBMA has also been evaluated in randomized controlled trials for use in the augmentation of anterior cruciate ligament reconstruction (ACL-R) and rotator cuff repair (RCR).[49,50] While these trials provide evidence suggesting improved biological tissue status resulting from the application of cBMA (greater ACL signal intensity on MRI at 3 months postoperatively; greater structural integrity of supraspinatus tendon repair at 1 year postoperatively), differences in clinically significant outcomes at short-term follow-up were inconsistently demonstrated. Collectively, this literature highlights the promise of bone marrow-derived therapy formulations, but further study is required to determine its definitive therapeutic benefit.

Adipose Tissue

In comparison to bone marrow, the stromal vascular fraction (SVF) derived from adipose tissue- may contain a higher relative concentration of MSCs (1-10% vs 0.001-0.01% of nucleated cells).[51,52] Adipose tissue-derived therapy formulations currently in clinical use are produced from mechanical processing (microfragmentation) and saline washing of autologous adipose tissue harvested through liposuction, typically from the abdomen. While this mechanism for processing meets the criteria for 'minimal manipulation,' it is notable that other means of processing, including the use of enzymatic digestion or culture expansion of adipose-derived tissue, do not, and are not covered under the FDA's 361 HCT/P pathway.[53–57]

The therapeutic effect of adipose-derived therapies is considered to largely result from a paracrine signaling effect of bioactive molecules (TGF-B, VEGF, FGF) rather than affecting tissue regeneration.[55] At present, there is some early evidence examining the clinical efficacy of adipose-derived cell therapies. While limited level 1 evidence exists, certain studies have suggested some therapeutic benefit from its use in the treatment of knee osteoarthritis and rotator cuff

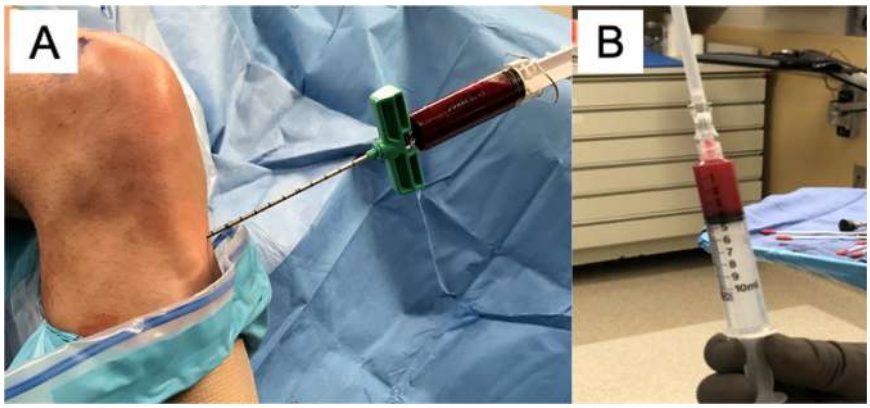

Figure 2 (A) Bone marrow aspiration being performed from the proximal tibia using a syringe connected to a trocar. (B) Final aspirate following centrifugation, demonstrating separation of the bone marrow concentrate with a visible buffy coat layer.

repair.[58–60] In a randomized controlled trial (RCT) comparing microfragmented adipose tissue to PRP for the treatment of knee osteoarthritis, Zaffagnini et al.[58] reported comparable clinical and radiographic outcomes with each modality at 2-year follow-up. When combined with arthroscopic debridement, Ulivi et al.[60] reported improved functional outcomes and T2-mapping scores on MRI with the application of microfragmented adipose tissue compared to arthroscopic debridement alone. Randelli et al.[59] also reported improvements in 6-month, but not longer-term clinical outcomes in a randomized controlled trial comparing rotator cuff repair with and without augmentation using microfragmented adipose tissue. Further study is necessary to more definitively demonstrate the therapeutic benefits of this orthobiologic agent, particularly at longer-term follow-up.

Perinatal Sources

Perinatal tissue sources, including amniotic fluid and membrane products, umbilical cord-derived products, placental tissue, and Wharton jelly have been proposed for orthobiologic treatment applications as a source of MSCs and biologic factors.[61,62] Other investigations into placental-derived tissue sources, specifically amniotic fluid, have failed to yield MSCs.[63] Presently, there is limited clinical application of perinatal tissue sources for orthobiologic treatment, as the nonhomologous nature, manipulation of tissue, and application outside of the native tissue function restrict its use to clinical trials under an IND application only.

Emerging Therapies

Exosomes

Research exploring the clinical utility of exosomes in the orthopedic literature continues to evolve.[64,65] Exosomes, by definition, are bilipid membrane molecules which serve as vesicles for signaling molecules, cytokines, lipids and microRNA.[66] The proposed benefit of such extracellular vesicle is to provide a transport mediator for MSC-associated therapies, mitigating the logistical challenges of cell procurement, culturing, processing, and delivery.[64]

There are no current FDA-approved exosome products available within the United States. There is ongoing preclinical research evaluating the beneficial effect of exosomes on cartilage regeneration,[67] inflammation attenuation of osteoarthritis,[68] tendon composition proliferation,[69] and muscle growth. There is potential for exosomes in the soft tissue regeneration realm, as evidenced by prior studies. The translation to a clinical meaningful product remains ongoing.

There are notable challenges with current exosome therapy. Difficulty with isolation and lack of molecular standardization both limit the ability to uniformly produce and study the effects of such therapy. There is inconsistency within the current literature regarding size, culture conditions, potency, and therefore effect.[65]

Induced Pluripotent Stem Cells

Stem cells, by definition, are unspecified cells that have the ability to divide asymmetrically in normal tissue.[70] They are multipotent cells with differentiating capacity. Mesenchymal stem cells are culture-expanded cells that, according to the International Society for Cell and Gene Therapy (ISCT), are cells that adhere to tissue culture plastic, have the capacity for differentiation in-vitro, and have the expression of specific cell-surface markers.[70,71] The goal of stem cell therapy is to modulate the immune and inflammatory environment of host tissue.[70] Culture expansion of cell therapy formulations currently is prohibited by the Food and Drug Administration (FDA), because it exceeded the definition of "minimal manipulation" by culture expansion and cell sorting.[72]

There is notable variation in culture-expanded cell populations, affecting both biologic activity and clinical efficacy. The proposed benefit of culture-expanded allogenic cell lines is the inherent homogeneity and selectivity that differs from the mixed starting population of progenitor cells.[70]

Cell-based therapy has been previously utilized for various tendinopathies, most notably patellar, rotator cuff, and Achilles tendinopathy, in an effort to improve the biologic milieu of the degenerative tendon. Early studies demonstrated improved rotator cuff tendon integrity and Achilles tendon healing with the addition of mesenchymal stem cells.[73–75] Jo et al.[75] demonstrated improved clinical outcomes and decreased retear rate compared to conventional repair. While there remains promise for cell therapy, there is little long-term evidence to support improved clinical outcomes. The current literature does not support the efficacy of stem cell therapy for tendon disorders in clinical practice.[76,77] Similarly, regarding osteoarthritis, current cell therapy approaches have not been demonstrated as superior to a corticosteroid injection.[78] Mautner et al.[78] called into question the role of exiting cell therapies, highlighting the need for further research. According to the Food and Drug Administration, stem cell therapy remains an Investigational New Drug (IND). Of promise is the use of allogeneic cultured maternal cord blood MSCs for the treatment of articular cartilage loss that will be initiating an FDA clinical trial in the U. S. in the near term.[79,80]

Extracellular Matrix Patch Scaffolds

Extracellular matrix scaffolds (ECMs) refer to the functional and structural components that support cellular organization and activity within tissues. Extracellular matrix patches scaffolds are available in biologic and synthetic options.[81] The goal of a scaffold is to provide both mechanical strength and biologic capability, yet current scaffolds demonstrate inferior strength to native tissue.[82]

Graft patches can be classified as xenografts, allografts, synthetic grafts, or a combination of the above.[81] Patch augmentation has been proposed for various tendinopathies, most notably rotator cuff repairs.[83–85] Dermal allografts demonstrated early promising results, particularly in the revision setting and with complex, irreparable rotator cuff

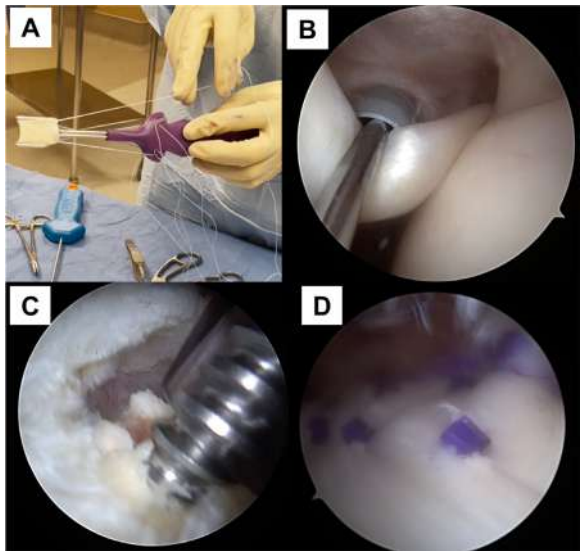

Figure 3 Dermal allograft patch in graft spreader (A) used to augment arthroscopic rotator cuff repair (B-C) with patch in place over repair (D).

tears.[86–89] Current literature is limited to retrospective case series.[88,90] Human dermal allograft augmentation has demonstrated superiority to xenograft augmentation for augmentation of large to massive rotator cuff repairs, yet there is heterogeneity in healing rates (Fig. 3).[90]

Purified Cytokines and Small Peptides

Injectable peptides are a regenerative therapeutic option that have been proposed for joint pathology and osteoarthritis.[91] Peptides are naturally-occurring signaling molecules that bind to surface receptors, and over 140 peptide therapeutics are being evaluated in clinical trials. Design, targets, and route of administration are being investigated.[92]

Therapeutic peptides aim to improve tissue and muscle repair, yet there is little orthopedic clinical literature to support their use. Common peptides under current investigation are collagen peptide supplementation, body protection compound 157, TB-500, Copper-binding peptide, ibutamoren, and CJC-1295.[91]

There is limited long term clinical evidence to support peptide-use. Dressler et al. evaluated the effectiveness of specific collagen peptide supplementation (SCP) in athletes with chronic ankle instability, demonstrating improved outcomes compared to controls.[93] The study was limited to subjective 6-month follow up, with potential confounding variables, including peptide type and administration. Lee and Padgett administered an intra-articular injection of BPC 157 for generalized knee pain in 16 patients, demonstrated variable levels of subjective improvement, highlighting the need for further high-quality studies.[94]

Of note, while BPC-157 has become more commercially available, it is prohibited by the World Anti-Doping Agency and by the NCAA.[95] Investigation is on-going, but randomized controlled trials supporting peptide use are not currently available.[91,96] There are no peptide products that are FDA-approved for soft tissue repair.

Repurposing of Existing Pharmaceutical Agents

Recent investigation has evaluated the efficacy of repurposing known FDA-approved compounds, with known mechanisms of action, for alternative uses.[70] Simvastatin has been demonstrated to promote the regeneration of an avascular meniscus in a rabbit model.[97] Yet high dose local administration of statins, by increasing the expression of bone morphogenetic protein 2 (BMP-2), have been demonstrated to negatively affect bone healing in an animal model.[98] Losartan, an angiotensin II receptor blocker, has antifibrotic properties, thus has been suggested for clinical use in arthroplasty and arthroscopic literature, with varying results.[99–101] Additionally, drugs that increase bone formation may be beneficial for tendon-bone interface healing, but further clinical studies are needed.[102]

Current Challenges

The lack of standardized nomenclature in the field of orthobiologics complicates both clinical application and research analysis. The frequent use of nonspecific terms such as “stem cells” without specifying their tissue of origin, their differentiation potential, and their specific role results in heterogeneity across studies, thereby limiting comparability and reproducibility.

Despite the abundance of studies available regarding orthobiologics, there are currently no existing protocols mandating their use. There exists significant variation in preparations and formulations, making the accurate measure of their effects limited. While PRP is subdivided into leukocyte-rich and leukocyte-poor PRP, fundamental aspects like the ratio of platelets to leukocytes or the presence of other signaling molecules remain unknown in such formulations. Consequently, the ability to discern therapeutic factors from inactive components becomes challenging.[103] While previous studies have determined clear benefits to the use of orthobiologics, there lacks consensus in high-level clinical trials.[15] High-quality, randomized controlled trials with standardized preparation formularies are needed to evaluate the long-term efficacy of the broad spectrum of treatment options encapsulated in orthobiologics.

Due to the lack of adherence to a specific therapeutic class (eg, drugs, devices, biologics), orthobiologics fall into a statutory ‘grey zone’ which complicates the regulatory status.[104] Additionally, variability in their use and outlook between countries results in discrepancies across regulatory bodies (eg, FDA in the USA, EMA in the European Union). Within the orthobiologic label itself, minimal manipulation and more-than-minimal-manipulation products may differ in their regulatory need.[105] Ongoing effort by regulatory bodies, such as the FDA and Biologics Association, are aiming to

provide clear frameworks and guidance for the utilization of orthobiologics in clinical practice.

Orthobiologics may be associated with a high upfront cost which limits their overall accessibility, particularly for low-income patients. Additionally, many of these treatment options are viewed as experimental by traditional insurers, resulting in the patient assuming the direct cost.[106,107]

Future Directions

Due to the promising nature of orthobiologics as a therapeutic modality, on-going investigation aims to establish standardized reporting frameworks across clinical studies and trials involving orthobiologics. Standardizing data collection for trials regarding orthobiologics is necessary to improve the quality of data produced, and in turn, the strength of the conclusions reached. Composition (autologous vs allogeneic), tissue of origin, dose and volume, composition (leukocytes, platelets, MSCs), biologic activity (quantification of cytokine activity or growth factors), purity, and preparation protocol are amongst the factors that must be quantified and reported. Terminology in these studies must become standardized to enable correct comparisons for both patients and orthopaedic providers both in the United States and abroad.

The studies in this paper highlight that the efficacy of orthobiologics is highly condition-dependent, with favorable outcomes in certain pathologies and limited effects in others. The future of orthobiologics relies on the ability to isolate specific characteristics that enable the efficacious use of orthobiologics and utilize them for conditions and patients that match these characteristics. The differentiation between the type of tissue, type of condition (degenerative, inflammatory, or traumatic), and the stage of disease progression, will enable a targeted, biomarker-driven strategy. For instance, inflammatory conditions mediated by TNF-α can specifically be targeted by matching biologic products to the pathophysiological mechanism at hand. Utilizing this personalized medicine approach will enable the most efficacious and targeted use of orthobiologics.

An important factor in the therapeutic success and minimization of side effects of orthobiologics is the ability to deliver a precise, localized, and controlled release of the therapeutic agent. It is vital to identify the target biologic target that is being treated. Nontargeted diffusion of orthobiologics such as BMPs can lead to ectopic bone formation and local inflammation, amongst other side effects.[108] While certain bioresorbable collagen materials have been developed to maximize localized efficacy, they can trigger adverse effects if released in too high concentrations. Though preferable to direct administration, these systems remain passive in nature, thereby maintaining their limitation of potentially diminished therapeutic efficacy. Future alternatives being explored is the initiation of 'smart biomaterials,' which exhibit controlled release kinetics.[109] Targeted carriers provide the ability to target treatment to affected malfunctional tissue, while keeping healthy tissue unaffected.[110]

Various orthobiologics have demonstrated early promising results, but mandate long-term clinical trials to support their use. Delivery vehicles, such as exosomes, provide cell-free alternatives with bioactive cargo, making them both scalable in production and available to the wider public.[111,112] Gene therapy remains under investigation due to its therapeutic potential. The delivery of genes encoding growth factors or anti-inflammatory agents would enable in-situ production of therapeutic proteins without the need for invasive procedures.

Ultimately, orthobiologics remain novel in nature which limits our ability to assess for the durability of their clinical benefits and side effects. While studies have been conducted to assess their efficacy and harms in the short-term, the number articles incorporating long-term follow up remain scarce. Ectopic bone production, chronic inflammation, immune responses, fibrosis, and tumorigenic risks associated with stem cells are all potential adverse events which need to be thoroughly assessed before making claims about the long-term safety and efficacy of orthobiologics.

Conclusion

Orthobiologics are a broad group of biologically-derived materials used to serve as, and augment, traditional musculoskeletal soft tissue and bone treatment options. These common symptom-modifying agents are becoming more frequently utilized in the sports medicine landscape as more is discovered about their potential and clinical applications. Blood-derived therapies, mesenchymal stem cell-derived therapies, extracellular matrix scaffolds, growth factors, and cell-based therapies are several of the common orthobiologics that show early promise. Although there are studies that demonstrate improvements in laboratory and patient outcomes, there is no 1 orthobiologic that is strongly recommended by governing orthopedic or federal healthcare bodies.

The future of orthobiologics will inevitably focus on standardizing both its research trials and data collection, as well as its nomenclature for both providers and patients. These treatment modalities have the potential to bring personalized and precision medicine to the orthopedic forefront; however, discovering ways to minimize side effects and orthobiologic failure is paramount to delivering high-value and cost-effective care. Ultimately, continued research is needed to establish clinical uses, adverse effects, cost effectiveness, long-term outcomes, and patient acceptance of orthobiologics.

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