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Mini Review

Orthobiologics: A New Frontier for Musculoskeletal Disease

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The past 20 years of medicine has seen an unprecedented rate of scientific discovery, providing a greater understanding of disease pathology and processes, eliciting a new area of medicine called "Orthobiologics". Orthobiologics have a specific emphasis on tissue healing and biological restoration by harnessing the regenerative potential within the body's own cells and redirecting their use for accelerated healing in damaged or diseased tissues. In the field of Sports Medicine, Orthobiologics have prompted a paradigm shift in treatment; from temporary symptomatic management to delay or disease prevention by modifying cell signals within the biologic environment. Many cellular therapies are evolving as a bridge between conservative non-invasive options and invasive surgical treatments. Thus far, Orthobiologics have experienced three generations of evolution, beginning with visco supplementation, or Hyaluronic Acid, progressing to Platelet Rich Plasma [1] and Bone Marrow Concentrate. Recent reports of Adipose and Umbilical Cord Derived Cells and specific growth factors such as BMP 7 [2] are now also found in the literature.

First generation Orthobiologics were available in the clinic in 1997 and consisted solely of Hyaluronic Acid (HA), a viscosupplementation for joint arthritis. HA reduced painful symptoms of osteoarthritis in those patients who responded to treatment and provided a superior safety profile when compared to continuous NSAID use for pain control [3-5].

Platelet Rich Plasma (PRP) didn't appear in the sports medicine literature until 2006; however, this 2nd generation of Orthobiologics was actually first used by Ferrari et al in 1987 following open heart surgery [6]. PRP was the first autologous Orthobiologic and used previously in many therapeutic areas including ENT, maxillofacial surgery, ophthalmology, urology, dentistry, cosmetic and neurosurgery as well as wound healing. Scientists studying wound healing discovered that platelets were not solely involved in clotting, but that they contained several bioactive proteins, such as stromal-derived factor 1α, as well as growth factors like TGFb-1, IGF-1, bFGF, BMP-2, etc., which encourage regenerative potential and healing properties [7,8]. Theoretically, the potent concentration of platelets are administered to stimulate a supra-physiologic response, as they are comprised of an undifferentiated cocktail of anti-inflammatory, pro-inflammatory, anabolic, and catabolic mediators in an attempt to elicit the body's natural healing response. Although, most of the literature consists of small case series [9,10], larger randomized controlled trials have demonstrated superior efficacy in areas such as tendinopathies [11,12] and knee osteoarthritis [13-16]. The authors recently published results of a multicenter, blinded controlled trial on leukocyte rich PRP use for lateral epicondylitis. Success rates for patients at 24 weeks post-treatment were 83.9% in the PRP group compared with 68.3% in the control group (P = .037) [11]. More recently, biologic injections have been applied to the spine. Prospective double blind randomized controlled data from the Hospital of Special Surgery (HSS) demonstrated improved outcomes with intra-discal PRP [17]. PRP injections for facet mediated joint pain have previously been described although warrants further clinical trials [18]. PRP applications will continue to expand with the growing volume of literature and mainstream publicity from PRP use in professional athletes; albeit, consistent guidelines for the variety of applications remain lacking. Standardization for optimal outcomes is needed to clarify which PRP preparation and protocol variables are best for which musculoskeletal conditions.

Bone Marrow Concentrate (BMC) is considered the 3rd generation of Orthobiologic therapy. See Figure 1. It has a potent mixture of mesenchymal stem cells (MSCs), hematopoetic cells, platelets, and cytokines noted for possessing anti-inflammatory, immunomodulatory, and chondrogenic properties, which act as the foundation for its regenerative potential [19]. Although the exact mechanism is unknown, it is hypothesized that the bone marrow concentrate mileau either induces differentiation and proliferation of resident stem cells, or possesses innate chondrogenic potential [19]. Dr. Caplan recently lectured at the 2014 (TOBI) The Orthobiologic Institute regenerative medicine symposium, suggesting that perivascular cells or Pericytes, adhere to blood vessels and act as one of our body's largest reservoirs for Mesenchymal Stem Cells. He explained that when the body undergoes trauma, soluble factors within the perivascular space cause the release of Pericytes from

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Figure 1: Harvesting of Bone Marrow Concentrate (BMC).

microvessels. Pericytes act as "Medicinal Signaling Cells" once released, where they can be activated into Mesenchymal Stem Cells, exhibiting trophic, immunomodulatory, and osteogenic roles. Dr. Caplan's research continues to expand our understanding of MSCs and provides insight into the potential therapeutic mechanisms of Mesenchymal Stem Cells [20].

The primary author recently presented clinical outcomes using BMC. 125 patients received hip, single knee, bilateral knees, shoulder, ankle, or cervical spine BMC injections. 87 patients had both pre- and post- injection pain scores available for review, of which 71% demonstrated a statistically significant reduction in overall pain at a median, follow up of 148 days. When comparing 87 with pre-post pain (complete) vs. 38 with pre or post missing (incomplete) data, there was no evidence of selection bias as both groups had similar variables (age, BMI, f/u time, satisfaction etc). Comparing statistically significant results from all treated regions revealed the single knee and bilateral knee injections had the largest improvement in pain score. Furthermore, 92% of patients reported satisfaction with the procedure and 95% of patients would recommend the procedure to a friend. Contrary to prior reports in the literature of an inverse relationship, age had no correlation with outcomes in this cohort of patients up to 79 years of age reporting positive results [21]. BMC therapy is also being used as an adjunct therapy post-operatively for procedures such as arthroscopic debridement, meniscal transplantation and subchondroplasty. Based on historical controls without use of BMC as an adjunct therapy, improved surgical results have been observed when a patient undergoes BMC treatment 2-3 weeks postoperatively [19].

Compared with BMC, adipose-derived MSCs, ADMSCs, are procured in much larger quantities with less invasive methods. ADMSCs continue to chondrogenic, osteogenic, adipogenic, myogenic, or neurogenic lineages. They have enhanced rates of proliferation, but show lesser responses to TGF-β-induced chondrogenesis [22]. Nevertheless, because of their facile procurement the use of ADMSCs is now being explored for various musculoskeletal applications.

In contrast with bone marrow or adipose-derived cells, umbilical cord-derived cells, UCDCs, have reduced isolation efficiency but expansion is more effective. Animal models using UCDCs triggered an inflammatory reaction in the synovium[23]; yet, there is a clinical trial at Rush University using UCDCs to treat cartilage defects. The results of this trial are anticipated.

To date, there is a paucity of level I evidence evaluating the therapeutic efficacy of BMC, as many of the studies are non-randomized, lack a control, and present only observational results of case series. Properly powered clinical trials and clinician collaboration is needed to further elucidate BMC as the 3rd generation of Orthobiologics and follow-up further on the use of ADSCs and UCDCs. Many queries remain polemical such as the ideal cell harvest technique, cell preparation as well as optimal window for various indications and injection protocols. Increased clinical use must not precipitate the responsibility to publish data and improve our understanding with controlled clinical trials. These early autologous therapies may serve as an introduction for more customized, refined cellular therapies incorporating the use of appropriate biomarkers to acquire knowledge of the mechanism of action as well as the optimal method of treatment.

References

1. Weglein A, Aufiero D, Sampson S. Platelet Rich Plasma: Practical Use in non surgical musculoskeletal patholgy. In: *Platelet Rich Plasma: Lecture Notes in Bioengineering*. Springer; 2014:187-201.
2. Sampson S, Gerhardt M, Mandelbaum B. Platelet rich plasma injection grafts for musculoskeletal injuries: a review. Curr Rev Musculoskelet Med. 2008;1: 165-174.
3. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. Bio Drugs. 2012; 26: 257-268.
4. Bannuru RR, Vaysbrot EE, Sullivan MC, McAlindon TE. Relative efficacy of hyaluronic acid in comparison with NSAIDs for knee osteoarthritis: A systematic review and meta-analysis. Semin Arthritis Rheum. 2013; 43: 593-599.
5. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis–meta-analysis. Osteoarthr Cartil. 2011; 19: 611-619.
6. Ferrari M, Zia S, Valbonesi M, et al. A new technique for hemodilution, preparation of autologous platelet-rich plasma and intraoperative blood salvage in cardiac surgery. Int J Artif Organs. 1987; 10: 47-50.
7. Anitua E, Sánchez M, Nurden AT, Nurden P, Orive G, et al. New insights into and novel applications for platelet-rich fibrin therapies. Trends Biotechnol. 2006; 24: 227-234.
8. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003; 83: 835-870.
9. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. Arthroscopy 2011; 27: 1490-1501.
10. Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil. 2012; 91: 411-417.
11. Mishra AK, Skrepnik NV, Edwards SG, Jones GL, Sampson S, et al. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. Am J Sport Med. 2014; 42: 463-471.
12. Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. Clin Rehabil. 2013; 27: 113-122.

13. Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012; 13: 229.

14. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sport Med. 2013; 41: 356-364.

15. Cerza F, Carnì S, Carcangiu A, Di Vavo I, Schiavilla V, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. Am J Sport Med. 2012; 40: 2822-2827.

16. Sánchez M, Fiz N, Azofra J, Aduriz Recalde E, Garcia Gutierrez A, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. Arthroscopy. 2012; 28: 1070-1078.

17. Lutz DG. Intradiscal PRP: A Prospective Double Blind Randomized Controlled Trial. Orthobiologic Inst PRP Regnerative Med Symp. 2014.

18. Aufiero D. How to Navigate Biologic Treatments of the Spine. Presented at the Annual Meeting of The Orthobiologic Institute (TOBI). 2014. Los Angeles, CA

19. Sampson S, Botto-van Bemden A, Aufiero D. Autologous bone marrow concentrate: review and application of a novel intra-articular orthobiologic for cartilage disease. Phys Sport. 2013; 41: 7-18.

20. Caplan A. MSCs: the New Medicine. Regenerative Medicine. Presented at the Annual Meeting of The Orthobiologic Institute (TOBI). 2014. Los Angeles, CA

21. Sampson S. Early Results with Bone Marrow Concentrate & Emerging Trends in Biologics. Presented at the Annual Meeting of The Orthobiologic Institute (TOBI). June 2014. Los Angeles, CA.

22. Huang JI, Kazmi N, Durbhakula MM, Hering TM, Yoo JU, et al. Chondrogenic potential of progenitor cells derived from human bone marrow and adipose tissue: a patient-matched comparison. J Orthop Res. 2005; 23: 1383–1389.

23. Yan H, Yu C. Repair of full-thickness cartilage defects with cells of different origin in a rabbit model. Arthroscopy 2007; 23: 178–187.

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