Level V Article

Biological Treatment for Osteoarthritis of the Knee: Moving from Bench to Bedside—Current Practical Concepts

Jorge Chahla, M.D., Ph.D., and Bert R. Mandelbaum, M.D., D.H.L. (hon.)

Abstract: Biological-based therapies for cartilage pathology have gained considerable recognition in the last few decades due to their potential benefits including their minimal invasiveness, capacity for unprecedented healing, and potential for rapid recovery. Consequently, these therapies are likely to have the most noteworthy impact on patients with degenerative joint changes who want to remain active. Currently, the most researched treatments include platelet-rich plasma (PRP), bone marrow aspirate concentrate (BMAC), and cell-based therapies. Although further basic science research and well-designed randomized clinical trials are needed to elucidate the long-term role of these therapies in the treatment of osteoarthritis, there is compelling evidence for their use for certain indications. This article aims to review the existing literature for biological-based treatment options for osteoarthritis, critically assessing the current evidence-based recommendations and identify potential avenues for development.

Osteoarthritis (OA) is not only a significant cause of morbidity, limitation to physical activity, and health care utilization, it is also a source of increased mortality.[1] A recent systematic review reported that patients with symptomatic hip or knee OA had 55% greater all-cause mortality compared with the general population. Additionally, a history of walking disability was associated with excess all-cause mortality and mortality due to cardiovascular disease, even after adjustment for age and sex.[2] Furthermore, OA also accounts for up to 18% of all health care visits in the United States,[3,4] which translates into an annual cost of more than $460 billion to the economy, secondary to lost wages and treatment costs.[5]

Currently, the most effective therapies for OA are prophylactic/preventative measures to avoid the development or slow the progression of the degenerative process (chondroprotection).[6] In this regard, it is vital to understand the concept of "chondropenia," which represents the early stage of degenerative cartilage disease. Chondropenia is not only the loss of articular cartilage volume, but it is also a rearrangement of biomechanical, ultrastructural, biochemical, and molecular properties typical of healthy cartilage tissue.[7] Hence, most of the therapies described herein will aid in chondrofacilitation—strategies that seek to facilitate intrinsic repair of damaged articular cartilage.[6]

As of now, no curative therapies for OA exist, and thus health care providers should acknowledge that management of OA should be directed toward pain control, function optimization, and, more importantly, therapies that can modify the natural history of the disease (disease-modifying therapies).[8-10] In recent years, there has been an exponential increase in the use of orthobiologics for the treatment of cartilage disease due to their minimal invasiveness, potential disease-modifying properties, and rapid recovery.[8,10,11] These include among others, platelet-rich plasma (PRP),[12-14] bone marrow aspirate concentrate (BMAC),[15-17] and the use of cell based-therapies.[18,19] Table 1 summarizes the source, Food and Drug Administration (FDA) status, and advantages/disadvantages of each of these therapies.

Despite the growing use of these biologic treatments, and the existing excitement and drive by both the medical and lay press, the body of literature lacks substantial evidence in regards to its indications, timing and

Santa Monica Orthopaedic and Sports Medicine Group, Santa Monica, California, U.S.A.

The authors report the following potential conflicts of interest or sources of funding: B.M. receives support from Arthrex, Depuy, Exactech, and Regen Biologics. Full ICMJE author disclosure forms are available for this article online, as supplementary material.

Received November 23, 2017; accepted January 26, 2018.

Address correspondence to Jorge Chahla, M.D., Ph.D., Santa Monica Orthopaedic and Sports Medicine Group, Kerlan Jobe Institute, Santa Monica, CA 90404, U.S.A. E-mail: jachahla@msn.com

0749-8063/171427/$36.00

https://doi.org/10.1016/j.arthro.2018.01.048

Table 1. Summary of the Source, Food and Drug Administration (FDA) Status, and Advantages/Disadvantages of Platelet-Rich Plasma (PRP), Bone Marrow Aspirate Concentrate (BMAC), and Stem Cells

	PRP	BMAC	Stem Cells
Source	Peripheral blood	Iliac crest (anterior superior iliac spine/posterior superior iliac spine)	Several sources (most common, bone marrow, adipose tissue)
FDA status (human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulation).	Regulated under section 361. Not required to obtain premarket approval/clearance from the FDA: the HCT/P is minimally manipulated and intended for homologous use only. The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent; and either (1) the HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or (2) the HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function and (a) is for autologous use, (b) is for allogeneic use in a first-degree or second-degree blood relative, or (c) is for reproductive use.		Regulated by the FDA under section 351 of the Public Health Service Act, which requires FDA approval of a Biologics License Application for permission to introduce, or deliver, a biologic product.
Pros	Easy to extract. Does not require sedation. Harvest and processing can be done in clinic. Compelling literature supporting its use for symptomatic treatment of osteoarthritis. Growing evidence of synergistic effects with hyaluronic acid. Can be prepared in multiple forms: activated/inactivated, liquid, and solid matrix. Concentration of platelets can be adjusted depending on the pathology.	No culture expansion. Same day procedure. No risk of allogeneic disease transmission. Low risk of infection. Higher concentration of interleukin-1 receptor antagonist blocked. Can be performed with concomitant procedures.	The underlying premise is that the arthritic knee may be deficient in a stem cell or progenitor cell population and that this deficiency may be mitigated by the harvest and transplantation of cells. Allogenic and autologous cell transplantation can be used. Several tissues types to isolate tissues from. Expanded and differentiated in culture under controlled settings. May be performed with concomitant procedures.
Cons	Potential inflammatory response to high platelet concentrations. No standardized method for intra-articular applications. No optimal preparation method. Potential detrimental effect of red blood cells when used in intra-articular environment. Heterogeneous solution that may indirectly affect other intra-articular tissues (interleukins, reactive oxygen species). Variable growth factor and cytokine quantities depending on several factors such as age, time of extraction, immune status, etc.	Potential pain during harvest with local anesthetic alone. Should be performed under sedation. Variable stem cell quantity and quality. No proven benefit over PRP as of now. Higher concentration of leukocytes and therefore greater inflammatory reaction. Potentially detrimental effect of erythrocytes when used in intra-articular environment.	Cells must be expanded ex vivo and require 4 to 6 weeks. Potential immunologic risk to patients. Risk of allogenic rejection. Safety concerns with proliferation of undesired lineages. Treatment restrictions set by the FDA. Limited understanding of the duration of transplanted cells.