

## American Association of Hip and Knee Surgeons Position Statement on Biologics for Advanced Hip and Knee Arthritis

An increasing number of facilities and physicians are offering intra-articular injections of stem cells and/or platelet-rich plasma (PRP) as a non-surgical treatment of advanced hip and knee osteoarthritis (OA) [1]. Administration of PRP injections in the United States increased more than 400% from 2010 to 2020 [2]. The global market for biologic injections is expected to become a multi-billion-dollar entity within the near future [3]. There are more than 40 commercial PRP systems in existence [4]; many of these systems were brought to market via the Food and Drug Administration (FDA) 510(k) pathway based on prior clearance of equivalent devices designed to mix PRP with bone graft [5]. As such, isolated PRP injections into a hip or knee joint are considered "off-label" by the FDA. Further, PRP and bone marrow aspirate concentrates (BMAC) are exempt from FDA regulation under Title 21, Part 1271 of the Code of Federal Regulations (21 CFR 1271) [5-7]. As a result, there is significant variability in the indications for use, preparation, processing, and administration of biologic treatments for the treatment of hip and knee OA across providers and practices.

As the popularity of biologic injections has increased, so has the breadth of patient education materials available online. Readily available information on biologic injections accessed via internet search engines is often targeted directly at the lay public suffering from hip or knee pain. However, this information is often incomplete and may be misleading to patients, with an emphasis on unsubstantiated benefits and a lack of information on potential risks or alternative treatments [8]. Direct-to-consumer marketing of BMAC as a "stem cell" therapy may further patient confusion [9]. While BMAC preparations usually contain extremely low concentrations (<0.01%) of mesenchymal stem cells (MSCs), such concentrations are much lower than those found in mesenchymal stem cells preparations that utilize culture expansion (e.g., adipose tissue-derived MSCs, umbilical cord blood-derived MSCs) [10, 11]. However, autologous blood products such as BMAC are not subject to FDA regulation, whereas stem cell preparations using culture expansion are subject to FDA regulation under 21 CFR 1271. Biologic injections are often not covered by insurance companies [2, 8], which may result in thousands of dollars of out-of-pocket costs for patients [12, 13].

Osteoarthritis is a slowly progressive degenerative disorder that involves damage to joint cartilage, structural changes in bone, and inflammation of the soft tissues around the joint [14]. Advanced arthritis involves complete loss of cartilage surface and exposure of subchondral bone (so-called "bone-on-bone arthritis"). Presently, there is no curative treatment for advanced hip and knee OA. Counter to claims made by individual providers or practices, biologic injections have not been shown to restore cartilage in hips and knees with OA [15-18].

Non-surgical treatments of advanced hip and knee OA are aimed at decreasing joint pain and improving joint function while avoiding the risks associated with total hip and total knee arthroplasty; biologic injections are no different. Recent prospective randomized controlled trials have failed to demonstrate a

significant benefit in pain or function of intra-articular PRP injections over intra-articular injections of saline placebo [15], corticosteroids [19], hyaluronic acid (HA) [20, 21], or genicular nerve radiofrequency ablation [22] in patients with advanced knee OA. Notably, there is limited evidence suggesting that PRP may be more efficacious than placebo and/or HA injections for the treatment of mild or moderate knee OA [23, 24]. Systematic reviews of level 1 and level 2 randomized controlled trials have demonstrated relatively equal efficacy of PRP and HA injections for patients with advanced hip OA [25]. Studies evaluating the efficacy of mesenchymal stem cells have demonstrated comparable results [17, 18]. While intra-articular injection of culture-expanded MSCs may offer a mild improvement relative to placebo [17], MSCs derived from multiple tissues sources have not been shown to be superior to corticosteroid injections for the treatment advanced knee OA [18].

Previous iterations of this position statement [26] questioned the safety of biologic injections. Reported complications of biologic injections have included injection site pain, hematoma formation, aseptic inflammatory response, and intra-articular infection [27-29]. Recent systematic reviews have demonstrated no difference in the safety profiles of injections of saline placebo and biologics [30]. Modern randomized controlled trials examining the use of PRP and/or mesenchymal stem cells [15, 17, 18] have demonstrated that biologic treatments can be administered without major adverse effects under rigorous safety protocols; however, it is paramount that the safety of biologic treatments be fully established before they can be supported for routine clinical use.

In conclusion, it is our position that biologic therapies, including injections of PRP, BMAC, or mesenchymal stem cells, cannot currently be recommended for the routine treatment of advanced hip or knee OA. This current position is largely unchanged from our prior position statement, published in 2019 [26]. A lack of data demonstrating significant improvements over existing non-biologic therapies and high out-of-pocket costs for patients preclude an endorsement of the routine use of biologics for the treatment of advanced hip and knee OA. We continue to encourage rigorous, well-designed clinical trials to further establish the safety, efficacy, and cost-effectiveness of biologic treatments prior to their widespread adoption.

## REFERENCES

1. Werner BC, Cancienne JM, Browning R, Verma NN, Cole BJ. An Analysis of Current Treatment Trends in Platelet-Rich Plasma Therapy in the Medicare Database. Orthop J Sports Med 8(2): 2325967119900811, 2020

2. Berlinberg EJ, Swindell H, Patel HH, Zabat M, Forlenza EM, Cancienne J, Forsythe B. The Epidemiology of Platelet-Rich Plasma Injections From 2010 to 2020 in a Large US Commercial Insurance Claims Database: A Recent Update. J Am Acad Orthop Surg 31(3): e135, 2023

3. Jones IA, Togashi RC, Thomas Vangsness C, Jr. The Economics and Regulation of PRP in the Evolving Field of Orthopedic Biologics. Curr Rev Musculoskelet Med 11(4): 558, 2018

4. Hsu WK, Mishra A, Rodeo SR, Fu F, Terry MA, Randelli P, Canale ST, Kelly FB. Platelet-rich plasma in orthopaedic applications: evidence-based recommendations for treatment. J Am Acad Orthop Surg 21(12): 739, 2013

5. Beitzel K, Allen D, Apostolakos J, Russell RP, McCarthy MB, Gallo GJ, Cote MP, Mazzocca AD. US definitions, current use, and FDA stance on use of platelet-rich plasma in sports medicine. J Knee Surg 28(1): 29, 2015

6. United States Department of Health and Human Services. Human cells, tissues, and cellular and tissue-based products. 21 CFR Part 1271. Available at:

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271. Accessed June 17, 2024.,

7. Lamplot JD, Rodeo SA, Brophy RH. A Practical Guide for the Current Use of Biologic Therapies in Sports Medicine. Am J Sports Med 48(2): 488, 2020

8. Shai SS, Shay RZ, Pretell-Mazzini J, Tal FR, Nir C, Barak H, Steven V. Platelet-Rich Plasma for Knee Osteoarthritis: Internet Marketing and Patient Education-An Appraisal of Content for Websites with the Greatest Search Engine Visibility. Cartilage 13(1\_suppl): 392S, 2021

9. Chu CR, Rodeo S, Bhutani N, Goodrich LR, Huard J, Irrgang J, LaPrade RF, Lattermann C, Lu Y, Mandelbaum B, Mao J, McIntyre L, Mishra A, Muschler GF, Piuzzi NS, Potter H, Spindler K, Tokish JM, Tuan R, Zaslav K, Maloney W. Optimizing Clinical Use of Biologics in Orthopaedic Surgery: Consensus Recommendations From the 2018 AAOS/NIH U-13 Conference. J Am Acad Orthop Surg 27(2): e50, 2019

10. Park YB, Ha CW, Rhim JH, Lee HJ. Stem Cell Therapy for Articular Cartilage Repair: Review of the Entity of Cell Populations Used and the Result of the Clinical Application of Each Entity. Am J Sports Med 46(10): 2540, 2018

11. Goodman SB, Zwingenberger S. Concentrated autologous bone marrow aspirate is not "stem cell" therapy in the repair of nonunions and bone defects. Biomater Biosyst 2: 100017, 2021

12. Piuzzi NS, Ng M, Kantor A, Ng K, Kha S, Mont MA, Muschler GF. What Is the Price and Claimed Efficacy of Platelet-Rich Plasma Injections for the Treatment of Knee Osteoarthritis in the United States? J Knee Surg 32(9): 879, 2019

13. Piuzzi NS, Ng M, Chughtai M, Khlopas A, Ng K, Mont MA, Muschler GF. The Stem-Cell Market for the Treatment of Knee Osteoarthritis: A Patient Perspective. J Knee Surg 31(6): 551, 2018

14. Buckwalter JA, Saltzman C, Brown T. The impact of osteoarthritis: implications for research. Clin Orthop Relat Res (427 Suppl): S6, 2004

15. Bennell KL, Paterson KL, Metcalf BR, Duong V, Eyles J, Kasza J, Wang Y, Cicuttini F, Buchbinder R, Forbes A, Harris A, Yu SP, Connell D, Linklater J, Wang BH, Oo WM, Hunter DJ. Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis: The RESTORE Randomized Clinical Trial. JAMA 326(20): 2021, 2021

16. Prodromidis AD, Charalambous CP, Moran E, Venkatesh R, Pandit H. The role of Platelet-Rich Plasma (PRP) intraarticular injections in restoring articular cartilage of osteoarthritic knees. A systematic review

and meta-analysis. Osteoarthr Cartil Open 4(4): 100318, 2022

17. Kim KI, Lee MC, Lee JH, Moon YW, Lee WS, Lee HJ, Hwang SC, In Y, Shon OJ, Bae KC, Song SJ, Park KK, Kim JH. Clinical Efficacy and Safety of the Intra-articular Injection of Autologous Adipose-Derived Mesenchymal Stem Cells for Knee Osteoarthritis: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial. Am J Sports Med 51(9): 2243, 2023

18. Mautner K, Gottschalk M, Boden SD, Akard A, Bae WC, Black L, Boggess B, Chatterjee P, Chung CB, Easley KA, Gibson G, Hackel J, Jensen K, Kippner L, Kurtenbach C, Kurtzberg J, Mason RA, Noonan B, Roy K, Valentine V, Yeago C, Drissi H. Cell-based versus corticosteroid injections for knee pain in osteoarthritis: a randomized phase 3 trial. Nat Med 29(12): 3120, 2023

19. Joshi Jubert N, Rodriguez L, Reverte-Vinaixa MM, Navarro A. Platelet-Rich Plasma Injections for Advanced Knee Osteoarthritis: A Prospective, Randomized, Double-Blinded Clinical Trial. Orthop J Sports Med 5(2): 2325967116689386, 2017

20. Kesiktas FN, Dernek B, Sen EI, Albayrak HN, Aydin T, Yildiz M. Comparison of the short-term results of single-dose intra-articular peptide with hyaluronic acid and platelet-rich plasma injections in knee osteoarthritis: a randomized study. Clin Rheumatol 39(10): 3057, 2020

21. Di Martino A, Di Matteo B, Papio T, Tentoni F, Selleri F, Cenacchi A, Kon E, Filardo G. Platelet-Rich Plasma Versus Hyaluronic Acid Injections for the Treatment of Knee Osteoarthritis: Results at 5 Years of a Double-Blind, Randomized Controlled Trial. Am J Sports Med 47(2): 347, 2019

22. Elawamy A, Kamel EZ, Mahran SA, Abdellatif H, Hassanien M. Efficacy of Genicular Nerve Radiofrequency Ablation Versus Intra-Articular Platelet Rich Plasma in Chronic Knee Osteoarthritis: A Single-Blind Randomized Clinical Trial. Pain Physician 24(2): 127, 2021

23. Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH. Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. Arthroscopy 35(1): 106, 2019

24. Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC. Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Am J Sports Med 49(1): 249, 2021

25. Belk JW, Houck DA, Littlefield CP, Kraeutler MJ, Potyk AG, Mei-Dan O, Dragoo JL, Frank RM, McCarty EC. Platelet-Rich Plasma Versus Hyaluronic Acid for Hip Osteoarthritis Yields Similarly Beneficial Short-Term Clinical Outcomes: A Systematic Review and Meta-analysis of Level I and II Randomized Controlled Trials. Arthroscopy 38(6): 2035, 2022

26. Browne JA, Nho SJ, Goodman SB, Della Valle CJ. American Association of Hip and Knee Surgeons, Hip Society, and Knee Society Position Statement on Biologics for Advanced Hip and Knee Arthritis. J Arthroplasty 34(6): 1051, 2019

27. Battaglia M, Guaraldi F, Vannini F, Rossi G, Timoncini A, Buda R, Giannini S. Efficacy of ultrasoundguided intra-articular injections of platelet-rich plasma versus hyaluronic acid for hip osteoarthritis. Orthopedics 36(12): e1501, 2013

28. Lim A, Zhu JB, Khanduja V. The Use of Intra-articular Platelet-Rich Plasma as a Therapeutic
Intervention for Hip Osteoarthritis: A Systematic Review and Meta-analysis. Am J Sports Med 51(9):
2487, 2023

29. Eliasberg CD, Nemirov DA, Mandelbaum BR, Pearle AD, Tokish JM, Baria MR, Millett PJ, Shapiro SA, Rodeo SA. Complications Following Biologic Therapeutic Injections: A Multicenter Case Series. Arthroscopy 37(8): 2600, 2021

30. Hong M, Cheng C, Sun X, Yan Y, Zhang Q, Wang W, Guo W. Efficacy and Safety of Intra-Articular Platelet-Rich Plasma in Osteoarthritis Knee: A Systematic Review and Meta-Analysis. Biomed Res Int 2021: 2191926, 2021

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## **Revised & Updated Statement**

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This statement is an expression of the policy of the American Association of Hip & Knee Surgeons. It is not a comprehensive review of the subject nor is it intended as medical advice for the treatment of individual patients.

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