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SPECIAL ISSUE: FRONTIERS IN SAFETY AND EFFICACY ON THE USE OF ORTHOBIOLOGIC TREATMENTS

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THE PURPOSE OF THIS SPECIAL ISSUE

This editorial provides an overview of the current medical literature regarding the safety and efficacy of orthobiologic procedures in the treatment of various orthopedic conditions presented in the special issue. The issue has been divided into sections of commonly used orthobiologic procedures. Several tables have been created to condense the literature, aiming to offer evidence-based insights to patients, clinicians, researchers, and regulatory and payer bodies concerned with the safety and effectiveness of these procedures. Ultimately, appropriate data and literature on the risks and benefits of any procedure are required before any conclusions related to these procedures can be reached. This should include clinical trials and data collected from independent registry databases focused on "real-world" data. This data will be essential to determine the ultimate value of orthobiologic procedures in treating orthopedic conditions to support the premise that these treatments are safe, effective, and robust alternatives to the many currently used orthopedic treatments.[1]

In the United States (US), the demand and costs for musculoskeletal care exceed available resources.[2] Amid the growing obesity epidemic and increased incidence of chronic comorbidities, the aging population is at substantial risk of developing chronic musculoskeletal disorders.[2] Health care expenditures accounted for 17.7% of the US gross domestic product (GDP) in 2018 and are expected to represent 19.7% by 2028.[3] For musculoskeletal disease, direct costs alone are expected to equal 5% of GDP and represent almost 30% of all healthcare expenditures.[2] In Medicare patients, osteoarthritis (OA) is a common condition and yet one of the most expensive conditions to treat.[4] In addition, many patients in the US, especially elderly patients, have several comorbidities which can result in an increased risk of potential complications, with a decreased likelihood of favorable outcomes following surgical procedures. Alternatives to current standard treatments are needed to provide treatment options for various patient populations suffering from orthopedic conditions, which includes both elderly patients with various medical comorbidities and the young and active population in which surgical treatment such as joint replacement may be premature.

OA is one of the leading causes of disability globally, and it is estimated that 14 million people in the United States have symptomatic knee OA.[5] It is the most common joint disorder in the USA and the incidence is likely to increase due to an aging population and the obesity epidemic. First-line treatment for patients with symptomatic knee OA involves conservative treatments, including exercise, weight loss, knee bracing, and physical therapy.[6] Medications and supplements that are

recommended often include: oral and topical nonsteroidal anti-inflammatory medications (NSAIDs), acetaminophen, duloxetine, glucosamine, and chondroitin.[7] Injectable options include corticosteroids and hyaluronic acid injections. These conservative treatment options have had various levels of success with mixed evidence for their efficacy.[8–10] Many patients have failed these various non-surgical treatments and fall into what has been described as the OA "Treatment gap." This is defined as the gap between a trial of conservative treatment and the potential need for surgical intervention. There are millions of Americans suffering from OA that sit in this "Treatment gap" for a decade or more. These include patients who are reluctant to proceed with surgery, patients who have other comorbidities that cannot undergo surgery, and patients that are felt to be too young to proceed with procedures such as joint replacement.[11]

Tendinopathy is another extremely common musculoskeletal condition. This can occur in both the young athletic population and middle-aged non-athletes. Tendinosis is histologically characterized as "angiofibroblastic hyperplasia" characterized by disorganized collagen matrix structure, hypercellularity, and neo-angiogenesis.[12,13]

While there is a paucity of acute inflammatory cells in biopsies from tendinopathy, it is currently understood that "molecular inflammation" plays a central role in tendinopathy, with numerous inflammatory mediators, chemokines, cytokines, and catabolic mediators playing critical roles in the initiation and regulation of the process, with important interactions between immune cell subtypes and stromal cells resident in tendon.[11,14] In fact, the important role of the complex interplay of inflammatory mediators is likely a reason for a positive effect on symptom modification when using these current treatments for tendinopathy. Based on this, a short course of nonsteroidal anti-inflammatories (~5-7 days) may be beneficial during the treatment's initial acute inflammatory phase. Similarly, although corticosteroids may offer short-term relief of symptoms, such injections may be more harmful in the long term. For example, a randomized controlled trial comparing corticosteroid injection to placebo in lateral epicondylitis found that the placebo group had a better outcome, and recurrence of symptoms was more significant in the corticosteroid-injected group at one year.[15] In addition, a systematic review demonstrated a lack of long-term efficacy of cortisone injections in lateral epicondylitis and rotator cuff, patellar, and Achilles tendinosis.[16] A recent study of patients with rotator cuff tendinitis illustrated a further concern, which noted that corticosteroid injections decrease cellular proliferation, alter collagen and extracellular matrix composition, impede inflammatory pathways, decrease cellular viability, increase adipocyte differentiation, and increase apoptosis. These changes were seen as early as 24 hours after corticosteroid exposure, last as long as 2 to 3 weeks, and are exacerbated by increased doses and decreased latency between doses.[17]

Over the past two decades, an increasing volume of medical research has questioned the safety and efficacy of many standard treatments for orthopedic conditions. This includes evidence regarding the efficacy of common treatments such as nonsteroidal anti-inflammatory medications, passive physical therapy treatments, corticosteroid (and other) injections, and some surgical procedures. For example, there is evidence that intra-articular corticosteroids are associated with an increased risk of radiographic knee OA progression.[18] A recent study also pointed out a lack of evidence for as many as 80% of all orthopedic surgical procedures.[19] Recently, some surgical procedures such as partial meniscectomy for degenerative meniscal tears,[20] subacromial decompression,[21] and labral repair or biceps tenodesis for type II SLAP lesions of the shoulder[22] are no better than sham surgery or conservative management. There are also variable outcomes for microfracture, a common surgical cartilage treatment.[23] In high-level athletes, microfracture was "successful" in only two-thirds of patients.[24] The questionable benefit of epidural corticosteroid injections has also been reported[25] and the appropriateness of spinal surgery has been questioned for low back pain.[26]

Injectable corticosteroids have been commonly used in treating various orthopedic conditions including tendinopathy and OA because of their anti-inflammatory effects. These compounds play a

key role in chemotaxis and inflammation, which is the rationale for their common use in orthopedic disorders. Unfortunately, recent literature suggests significant negative side effects of these medications. A single epidural corticosteroid injection has been shown to decrease bone density[27] and increase the risk of spinal fractures.[28] There is also evidence of corticosteroid injections resulting in systemic effects such as immune suppression, including an increased risk of contracting influenza.[29] Intra-articular corticosteroid injections for knee OA provide temporary benefit, with most studies reporting two weeks and perhaps modest benefit remaining at eight weeks.[30] Recent clinical evidence[18] highlights risks of disease progression, where a randomized controlled trial[31] suggested that intra-articular corticosteroid injections decrease cartilage volume and accelerate OA. Although intra-articular corticosteroid injections may provide significant benefit in the short term, other treatment options are clearly necessary. These data make clear both the need for alternative treatment approaches and the tremendous potential for them.

THE POTENTIAL OF ORTHOBIOLOGIC TREATMENTS

The potential role of orthobiologic treatments such as platelet-rich plasma (PRP), bone marrow and adipose cellular procedures, etc., is to treat pain via the effect of anti-inflammatory mediators and immune-modulating signaling molecules and to possibly enhance the healing of tissue pathology by augmenting the body's inherent healing capabilities. The use of orthobiologic treatments has often been referred to as "regenerative medicine" which includes multiple techniques ranging from prolotherapy to PRP and cellular procedures including mesenchymal stromal cell (MSC) therapy. Multiple sources of stem and stromal cells have been used for various medical conditions, ranging from human adult tissues, umbilical and other birth tissues, and embryonic stem cells. Embryonic stem cell therapy is subject to significant regulatory and ethical issues with potentially adverse effects. Currently, no studies support the use of embryonic stem cell therapy for orthopedic conditions. Human adult stem cells have been located from various tissues, including blood, adipose, bone marrow, and synovial tissue. In-vitro, the multipotent nature of MSCs allows differentiation into diverse cell types in the mesenchymal lineage, including bone, cartilage, adipose, and other soft tissues. It should be noted that true tissue formation in-vivo using culture-expanded cells has proven elusive. The lure of tissue "regeneration" has largely not been demonstrated in pre-clinical and clinical studies. It should be made clear that the positive effects of cell transplantation occur without long-term engraftment or survival of transplanted cells, but rather due to the presumed paracrine effects of cells.[13]

Currently, literature supporting what many authors have referred to as "stem cell" therapies for orthopedic conditions includes basic science and animal studies. Human clinical studies include case reports, case series, cohort studies, and several recent randomized controlled trials. Many laboratory and clinical scientists have questioned the safety and efficacy of such treatments. In particular, those labeled as "stem cell therapies" have attracted great scrutiny. These concerns have permeated academic journals and the mainstream media through newspaper articles and editorials. Also, due to the indiscriminate use and aggressive marketing, the FDA has issued stringent guidance statements and expressed concerns on its website and in publications in medical journals regarding regenerative treatments in general. This has led some authorities to recommend against offering these treatments.

The majority of the negative articles and editorials regarding regenerative medicine and stem cell therapy have focused on a handful of highly publicized cases unrelated to orthopedic care, such as intraocular injection of adipose-derived cells.[32,33] Although intra-articular infections have been reported, the overwhelming majority of the significant adverse events relating to stem cell treatments have occurred in non-orthopedic conditions or injecting non-FDA-compliant tissues harvested from birth tissue. Cases with tumor formation appear to be due to embryonic stem cell treatment.[34] or treatment with unusual cell lines,[35] which are not used in orthopedic procedures. Tumorigenic effects have

not been found to occur when using autologous tissues such as bone marrow aspirate concentrate (BMAC).[36] There have been no unusual side effects secondary to localized treatments for orthopedic conditions besides typical side effects that can occur with standard injection procedures. Infections have been noted following injection of contaminated non-FDA compliant products from allogenic sources such as umbilical cord.[37] The overall body of literature on the safety of "orthobiologics" continues to include detailed adverse event reporting.[38] Ongoing data collection would be helpful in this regard.

The term "Regenerative Medicine" has been commonly used and accepted by prominent organizations such as the International Cartilage Repair Society (ICRS), and even the FDA has used this term on its website. Therefore, this term has been intermittently used in this project, although it is not preferred due to the controversy related to this terminology. There have been misconceptions regarding the potential "regenerative" capabilities of these treatments in-vivo with the concept that MSCs differentiate into various tissue types following either intravenous or local injection. The term "mesenchymal stem cell" has been commonly and improperly used in many articles, being applied to cell populations that vary tremendously in biologic activity.[39] A more scientific and up-to-date literature review would note that most of these cellular treatments contain very few "stem cells" when carefully examined by cellular, molecular, or functional criteria in adult/mature tissues. A more acceptable term, "connective tissue progenitors" (CTPs), would appear to be more appropriate, representing a population of cells present in freshly harvested tissues that are capable of (limited) proliferation to generate a clonal population of progeny that are subsequently capable of differentiating into at least one or more connective tissue phenotypes (in cell culture).[40] The term MSC should only be used to refer to a culture-expanded population of cells that meet the International Society for Cell & Gene Therapy (ISCT) and MSC criteria and should not be used to describe heterogeneous populations of native cells with undefined properties in-vivo.[41] However, Dr. Arnold Caplan, who initially coined the term MSC, has proposed that this term refer to "Medicinal Signaling Cells" to recognize the paracrine effect of exogenous cells.[42] This would again appear to be a more accurate description of the cells, especially in the in-vivo environment. Current scientific evidence reflects that injected cells may modify the local tissues' microenvironment by modulating various inflammatory and nociceptive cytokines and possible facilitation of local tissue healing. The term "orthobiologic treatments" has also been used to describe these treatments. PRP, BMAC, and adipose-derived cells are particularly interested in treating sports injuries, especially given the potential adverse effects of commonly used treatments, such as anti-inflammatory medications and corticosteroid injections. In light of these issues, using biological treatments, such as a patient's cells and growth factors, to heal damaged tissues is an attractive option. In conjunction with aggressive and comprehensive rehabilitation, these treatments may maximize the non-surgical treatment of these various sports and non-athletic orthopedic conditions. However, the initial evidence of safety requires more long-term follow-up including detailed adverse event reporting.[38]

CONCLUSION

This special issue has provided an overview of the current medical literature regarding the safety and efficacy of orthobiologic procedures in treating various orthopedic conditions. Individual reviews will include platelet-rich plasma, adipose, bone marrow, amniotic, other birth tissue-derived therapies, and a cost and outcomes analysis.

There is clear evidence of safety when these procedures are performed using appropriate products, indications, and methods. Evolving evidence of efficacy for these procedures has progressively increased in number and level of evidence over time. Clear evidence supports PRP for mild to moderate knee and hip arthritis, and strong evidence exists for its effectiveness in treating tendinopathies. Bone marrow and adipose cell treatments are safe and effective for knee osteoarthritis and rotator cuff issues, with some evidence for other conditions. Based on this evidence, it's advisable to consider these regenerative

treatments in conversations about managing musculoskeletal conditions. Regenerative medicine brings a safe, effective, and financially responsible approach to improve outcomes in musculoskeletal conditions, which continue to burden the current US healthcare system socially and financially.

REFERENCES

1. Jenio FZ, Scholes C, Marenah M, Li J, et al. Quality in practice: implementation of a clinical outcomes registry in regenerative medicine. Ann Trans Med; 2019;7(7). https://doi.org/10.21037/atm.2019.02.38
2. Yu S and Zuckerman J. 5 Points on Orthopedics in US Health Care. Am J Orthop 2015;44:12.
3. Hartman M, Martin AB, Espinosa N, et al. National health care spending in 2016: spending and enrollment growth slow after initial coverage expansions. Health Affairs 2018;37(1):150–160. https://doi.org/10.1377/hlthaff.2017.1299
4. Cutler DM, and Ghosh K. The potential for cost savings through bundled episode payments. New Engl J Med 2012;366(12):1075. https://doi.org/10.1056/NEJMp1113361
5. Vina ER and Kwoh CK. Epidemiology of osteoarthritis: literature update. Curr Opin Rheumatol 2018;30(2):160. https://doi.org/10.1097/BOR.0000000000000479
6. Hsu H and Siwiec R. Knee Osteoarthritis. [Updated 2019 Jun 17]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019.
7. Vaishya R, Pariyo GB, Agarwal AK, and Vijay V. Non-operative management of osteoarthritis of the knee joint. J Clin Orthop Trauma 2016;7(3):170–176. https://doi.org/10.1016/j.jcot.2016.05.005
8. Miller LE, Fredericson M, Altman RD. Hyaluronic acid injections or oral nonsteroidal anti-inflammatory drugs for knee osteoarthritis: systematic review and meta-analysis of randomized trials. Orthop J Sports Med. 2020 Jan 27;8(1):2325967119897909. https://doi.org/10.1177/2325967119897909
9. Kon E, Filardo G, Drobnic M, Madry H, Jelic M, van Dijk N, Della Villa S. Non-surgical management of early knee osteoarthritis. Knee Surg Sports Traumatol Arthroscop 2012 Mar;20:436–49. https://doi.org/10.1007/s00167-011-1713-8
10. Parker DA, Scholes C, Neri T. Non-operative treatment options for knee osteoarthritis: current concepts. Journal of ISAKOS. 2018 Sep 1;3(5):274–81. https://doi.org/10.1136/jisakos-2016-000094
11. London NJ, Miller LE, and Block JE. Clinical and economic consequences of the treatment gap in knee osteoarthritis management. Med Hypotheses 2011;76(6):887–892. https://doi.org/10.1016/j.mehy.2011.02.044
12. Malanga G and Nakamura R. The role of regenerative medicine in the treatment of sports injuries. Phys Med Rehabil Clin 2014;25(4):881–895. https://doi.org/10.1016/j.pmr.2014.06.007
13. Malanga G and Goldin M. PRP: review of the current evidence for musculoskeletal conditions. Curr Phys Med Rehab Rep 2014;2(1):1–15. https://doi.org/10.1007/s40141-013-0039-5
14. Tang C, Chen Y, Huang J, et al. The roles of inflammatory mediators and immunocytes in tendinopathy. J Orthopaed Transl 2018;14:23–33. https://doi.org/10.1016/j.jot.2018.03.003
15. Coombes BK, Bisset L, and Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. The Lancet 2010;376(9754):1751–1767. https://doi.org/10.1016/S0140-6736(10)61160-9
16. Coombes BK, Bisset L, Brooks P, et al. Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondylalgia: a randomized controlled trial. JAMA 2013;309(5): 461–469. https://doi.org/10.1001/jama.2013.129
17. Puzzitiello RN, Patel BH, Forlenza EM, et al. Adverse impact of corticosteroids on rotator cuff tendon health and repair: a systematic review of basic science studies. Arthroscop Sports Med Rehabil 2020;2(2):e161–e169. https://doi.org/10.1016/j.asmr.2020.01.002
18. Zeng C, Lane N, Hunter D, et al. Intra-articular corticosteroids and the risk of knee osteoarthritis progression: results from the Osteoarthritis Initiative. Osteoarthritis and Cartilage 2019; 27(6), 855–862. https://doi.org/10.1016/j.joca.2019.01.007
19. Lohmander LS and Roos EM. The evidence base for orthopaedics and sports medicine: scandalously poor in parts. Br J Sports Med 2016;50(9):564–565. https://doi.org/10.1136/bjsports-2016-g7835rep
20. Sihvonen R, Paavola M, Malmivaara A, et al. Arthroscopic partial meniscectomy versus sham surgery for a degenerative meniscal tear. N Engl J Med 2013;369:2515–2524. https://doi.org/10.1056/NEJMoa1305189
21. Paavola M, Malmivaara A, Taimela S, et al. Subacromial decompression versus diagnostic arthroscopy for shoulder impingement: randomised,

placebo-controlled clinical trial. BMJ 2018;362. https://doi.org/10.1136/bmj.k2860
22. Schrøder CP, Skare Ø, Reikerås O, et al. Sham surgery versus labral repair or biceps tenodesis for type II SLAP lesions of the shoulder: a three-armed randomised clinical trial. Br J Sports Med 2017;51(24):1759–1766. https://doi.org/10.1136/bjsports-2016-097098
23. Erggelet C and Vavken P. Microfracture for the treatment of cartilage defects in the knee joint-A golden standard? J Clin Orthopaed Trauma 2016;7(3):145–152. https://doi.org/10.1016/j.jcot.2016.06.015
24. Gudas R, Kalesinskas RJ, Kimtys V, et al. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. Arthroscopy: J Arthroscop Related Surg 2005;21(9): 1066–1075. https://doi.org/10.1016/j.arthro.2005.06.018
25. Koes BW, Scholten RJ, Mens JM. and Bouter LM. Efficacy of epidural steroid injections for low-back pain and sciatica: a systematic review of randomized clinical trials. Pain 1995;63(3):279–288. https://doi.org/10.1016/0304-3959(95)00124-7
26. Bogduk N and Andersson G. Is spinal surgery effective for back pain? F1000 Medicine Reports 2009;1. https://doi.org/10.3410/M1-60
27. Al-Shoha A, Rao DS, Schilling J, et al. Effect of epidural steroid injection on bone mineral density and markers of bone turnover in postmenopausal women. Spine 2012;37(25):E1567–E1571. https://doi.org/10.1097/BRS.0b013e318270280e
28. Mandel S, Schilling J, Peterson E, Rao DS, Sander W. J Bone Joint Surg Am 2013 Jun 5;95(11):961–4. https://doi.org/10.2106/JBJS.L.00844
29. Sytsma TT, Greenlund LK, and Greenlund LS. Joint corticosteroid injection associated with increased influenza risk. Mayo Clinic Proceedings: Innovat Qual Outcome 2018;2(2):194–198. https://doi.org/10.1016/j.mayocpiqo.2018.01.005
30. Cato RK. Indications and usefulness of common injections for nontraumatic orthopedic complaints. Medical Clinics 2016;100(5):1077–1088. https://doi.org/10.1016/j.mcna.2016.04.007
31. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis: a randomized clinical trial. JAMA 2017;317(19), 1967–1975. https://doi.org/10.1001/jama.2017.5283
32. Rong AJ, Lam BL, Ansari ZA, Albini TA. Vision Loss Secondary to Autologous Adipose Stem Cell Injections: A Rising Problem. JAMA Ophthalmol 2018 Jan 1;136(1):97–99. https://doi.org/10.1001/jamaophthalmol.2017.5453
33. Kuriyan AE, Albini TA, Townsend JH, et al. Vision Loss after Intravitreal Injection of Autologous "Stem Cells" for AMD. N Engl J Med. 2017 Mar 16;376(11):1047–1053. https://doi.org/10.1056/NEJMoa1609583
34. Amariglio N, Hirshberg A, Scheithauer BW, et al. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med 2009;6(2), e1000029. https://doi.org/10.1371/journal.pmed.1000029
35. Dlouhy BJ, Awe O, Rao RC, Kirby PA, Hitchon PW. Autograft-derived spinal cord mass following olfactory mucosal cell transplantation in a spinal cord injury patient: Case report. J Neurosurg Spine. 2014 Oct;21(4):618–22. https://doi.org/10.3171/2014.5.SPINE13992
36. Centeno CJ, Al-Sayegh H, Freeman MD, et al. A multi-center analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions. Internat Orthopaed 2016;40:1755–1765.https://doi.org/10.1007/s00264-016-3162-y
37. Perkins KM, Spoto S, Rankin DA, et al. Infections after receipt of bacterially contaminated umbilical cord blood-derived stem cell products for other than hematopoietic or immunologic reconstitution-United States, 2018. Morbid Mortal Weekly Rep 2018;67(50):1397–1399. https://doi.org/10.15585/mmwr.mm6750a5
38. Marenah M, Li J, Kumar A, Murrell W. Quality assurance and adverse event management in regenerative medicine for knee osteoarthritis: Current concepts. J Clin Orthopaed Trauma 2019;10(1), 53–58. https://doi.org/10.1016/j.jcot.2018.09.005
39. Pittenger M, Discher D. Pérault BM, et al. Mesenchymal stem cell perspective: cell biology to clinical progress. NPJ Regenerat Med 2019;4:22. https://doi.org/10.1038/s41536-019-0083-6
40. Rodeo S. Stem Cells 101. Am J Sports Med 2021;49(6):1417–1420. https://doi.org/10.1177/03635465211011082
41. Horwitz EM, Le Blanc K, Dominici M, et al. Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. Cytotherapy 2005;7(5):393–395. https://doi.org/10.1080/14653240500319234
42. Caplan AI. Mesenchymal stem cells: time to change the name! Stem Cells Translational Med 2017;6(6):1445–1451. https://doi.org/10.1002/sctm.17-0051