2019-2020 NFL and NFL Physician Society Orthobiologics Consensus Statement

Scott A. Rodeo, MD,[†‡§||] and Asheesh Bedi, MD*[¶#]

Keywords: orthobiologics; PRP; stem cells; National Football League (NFL)

"Biologic therapies" encompass techniques such as the injection of platelet-rich plasma (PRP) and the collection and injection of progenitor "stem" cells derived from bone marrow, amnion, or fat tissue. The underlying rationale for use of these techniques is the potential to improve symptoms and to possibly augment healing of tissues that have relatively poor intrinsic healing ability such as cartilage, tendon, ligament, bone, muscle, and meniscus. Although basic science data suggest strong potential for these approaches to improve tissue healing, there are currently only limited clinical data to support use of these techniques for treatment of musculoskeletal conditions. A large number of unproven therapies are being marketed directly to athletes, with unsubstantiated claims of efficacy and lack of information about risks, product manufacturing, and realistic expectations of outcomes.[2,14,15]

It is critically important to understand and distinguish the safety and effectiveness of these treatments from unsubstantiated claims and promises. Biological treatments must have appropriate indications and must be prepared with meticulous and sterile processing to minimize the risk of infection or other adverse effect.

PLATELET-RICH PLASMA

PRP is produced by centrifugation ("spinning down") of a small sample of the patient's blood to isolate and concentrate the platelets. Both platelets and plasma (the fluid portion of blood) contain a number of proteins that can potentially decrease inflammation, improve pain, and aid in tissue healing. PRP has been used for many soft tissue injuries, including ligament, tendon, meniscus, cartilage, and muscle. However, at this time there are only rigorous data to support the use of specific PRP formulations for (1) symptoms of osteoarthritis of the knee and (2) chronic tendinitis of the patellar tendon ("jumper's knee") and elbow extensor tendons ("tennis elbow"). PRP has *not* been reliably shown to regenerate cartilage or improve healing of tendon or meniscal repairs.[1,4,6-8,10,12]

PRP is generally safe since it is derived from the patient's own blood. The major limitation of PRP is the significant unpredictability in its effect because of the wide variability in different PRP formulations and lack of information about the optimal PRP formulation for different conditions. Further information is required to define the specific type of PRP that will be most effective for a specific condition or injury. For example, important factors include the platelet concentration, the presence or absence of white blood cells, the type of white blood cells, the ratio between different cell types, and so on. Indiscriminate use of the same type of PRP for widely different injuries and conditions has contributed to the unpredictable and variable outcomes. The lack of strong clinical data supporting efficacy of PRP is the reason that most medical insurance companies do not cover the cost of PRP therapy.[1,4,6-8,10,12]

CELL-BASED THERAPY

There is much hype and controversy about "stem cells" for healing and regeneration of numerous different tissues. Stem cells are defined by the ability to undergo self-renewal and to regenerate other types of cells and tissues. The use of stem cells for treatment of numerous conditions has received increasing publicity in print and social media, leading many athletes to pursue these treatments. Cell therapy has great potential for

From [†]Hospital for Special Surgery, Co-Chief Emeritus, Sports Medicine Institute, Hospital for Special Surgery, New York, New York, [‡]Weill Cornell Medical College, New York, New York, [§]New York–Presbyterian Hospital, New York, New York, [||]New York Giants, East Rutherford, New Jersey, [¶]Sports Medicine, Sports Medicine & Shoulder Surgery, MedSport, Department of Orthopaedic Surgery, Michigan Medicine, University of Michigan Athletics, Ann Arbor, Michigan, and [#]Detroit Lions, Detroit, Michigan
*Address correspondence to Asheesh Bedi, MD, Harold and Helen W. Gehring Professor, Chief, Sports Medicine, Sports Medicine & Shoulder Surgery, MedSport, Department of Orthopaedic Surgery, Michigan Medicine, Head Orthopaedic Team Physician, University of Michigan Athletics, 24 Frank Lloyd Wright Drive, MedSport, Suite 1000, Lobby A, Ann Arbor, MI 48105 (email: abedi@med.umich.edu).

The following authors declared potential conflicts of interest: S.A.R. is a consultant for Flexion Therapeutics and Teladoc Health and has stock options from Ortho RTI. A.B. is a consultant for and receives royalties from Arthrex.
DOI: 10.1177/1941738119889013

tissue healing and regeneration, but there remain many outstanding questions at this time. There is *no* high-quality evidence available at this time to support the routine use of stem cell therapy for any musculoskeletal injuries.

Currently, stem cells can be isolated from bone marrow and fat. However, the number of stem cells in both bone marrow and fat is very small—only approximately 1 in 10,000. In this regard, the number of viable (living) cells that are actually delivered and survive injection into a new environment is unknown. Effective use of stem cells requires the cells to be transported to a laboratory for cell isolation and culture expansion to increase the number of stem cells. However, the Food and Drug Administration (FDA) in the United States does not allow such laboratory processing of cell preparations. The "minimally manipulated" cell preparations used in the United States, whether in the clinic or the operating room, should be distinguished from laboratory-prepared cells. The "stem cell" preparations offered at numerous clinics in the United States contain very few true stem cells by formal criteria.[5,9,11,13]

Cell culturing to increase the number of available cells is permitted in several other countries, leading individuals to sometimes seek these treatments overseas ("medical tourism"). The risk of this practice is that the standards for cell processing and manufacturing in other countries are unknown and are often not as rigorous as standard protocols in the United States. Serious adverse side effects and complications have been reported, including severe infections. Although there are legitimate cell therapy centers overseas, the specific details of their treatment protocols, how the cells are processed, and what other materials are injected with the cells are often unknown, adding to the uncertainty and risk.

There exist some very limited data to suggest that cells derived from bone marrow and fat tissue may improve symptoms from osteoarthritis of the knee, likely due to the production of anti-inflammatory chemicals by the cells. However, there are essentially no data to suggest that the uncultured cell therapy techniques currently available in the United States can lead to any tissue regeneration. Many of the marketing claims made about the efficacy of stem cell therapy are based on data using cultured cells, and data on currently available cell preparations in the United States strongly suggest that this is false and misleading.

Cell-based therapies have tremendous potential for treatment of numerous injuries and diseases. However, much more research is required to identify the optimal cell types, cell processing techniques, cell dosing schedules, methods to localize and retain the cells at the desired site after injection, and postinjection protocols. Also needed are standards that define the criteria used to characterize cell populations, along with uniform reporting of those criteria in research studies.[3,5,9,11,13]

CURRENT REGULATORY ENVIRONMENT FOR REGENERATIVE MEDICINE

The widespread use of inappropriate direct-to-consumer marketing of unproven cellular therapies has recently led to increased scrutiny from the US FDA. New guidelines have been published by the FDA that are aimed at curtailing the inappropriate marketing and use of "regenerative medicine" approaches in the United States, including cell-based therapies and blood-based derivatives such as PRP. Unsubstantiated claims of efficacy as well as the use of cell and blood processing techniques that go beyond the "minimal manipulation" allowed by the FDA have led to official warning letters and even closure of some "stem cell" and "regenerative medicine" centers. At the same time, these new FDA regulations will also help accelerate the approval pathway for *legitimate* therapies after appropriate clinical trials.[2,3,5,9,11,13-15]

WHAT NFL TEAM PHYSICIANS ARE DOING IN THE AREA OF REGENERATIVE MEDICINE

National Football League (NFL) team physicians recognize the tremendous potential of these treatment options for numerous difficult-to-treat conditions, such as muscle strain injury, tendon injury, cartilage repair and regeneration, degenerative disc disease in the spine, delayed or failed healing of difficult fractures, and healing after ligament or meniscal repair.

NFL team physicians have extensive experience with managing these conditions and studying the underlying scientific issues, and thus we fully understand the *potential* and *limitations* of current regenerative medicine approaches. NFL team physicians are committed to studying and reporting the use of regenerative medicine approaches in a responsible and rigorous fashion. Recognizing that many athletes can gain relief with these generally safe therapies, we aim to use these treatments in the appropriate clinical situations. To further this effort, we aim to carefully track outcomes of treatment with various agents. We believe that responsible use of regenerative medicine treatments is the best way to both provide cutting-edge care for our athlete-patients and to also contribute to the knowledge base in order to advance this rapidly developing field.

SUMMARY KEY POINTS

- Orthobiologic treatments, such as PRP and "stem cells", offer promise for pain relief and potentially improved healing of certain conditions affecting tendons, ligaments, and joints.
- The indications for use and the claims reporting tissue regeneration after PRP or stem cell therapy are not supported by the available evidence at this time.
- Indiscriminate use of orthobiologic treatments and/or lack of rigorous protocols for tissue processing and delivery can paradoxically put athlete health and safety at risk.
- Active research studies by scientists will help define the best indications and applications for biologic therapies that maximize both the benefit and safety for our athletes.

REFERENCES

1. Andriolo L, Altamura SA, Reale D, Candrian C, Zaffagnini S, Filardo G. Nonsurgical treatments of patellar tendinopathy: multiple injections of platelet-rich plasma are a suitable option: a systematic review and meta-analysis. *Am J Sports Med*. 2019;47:1001-1018.

2. Bauer TW. Stem cell therapy for knee pain—what exactly are we injecting, and why? *J Bone Joint Surg Am*. 2016;98:1509-1510.
3. Chahla J, Cinque ME, Piuzzi NS, et al. A call for standardization in platelet-rich plasma preparation protocols and composition reporting: a systematic review of the clinical orthopaedic literature. *J Bone Joint Surg Am*. 2017;99:1769-1779.
4. Dai WL, Zhou AG, Zhang H, Zhang J. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. *Arthroscopy*. 2017;33:659-670.e1.
5. Deans RJ, Moseley AB. Mesenchymal stem cells: biology and potential clinical uses. *Exp Hematol*. 2000;28:875-884.
6. Dupley L, Charalambous CP. Platelet-rich plasma injections as a treatment for refractory patellar tendinosis: a meta-analysis of randomised trials. *Knee Surg Relat Res*. 2017;29:165-171.
7. Fitzpatrick J, Bulsara M, Zheng MH. The effectiveness of platelet-rich plasma in the treatment of tendinopathy: a meta-analysis of randomized controlled clinical trials. *Am J Sports Med*. 2017;45:226-233.
8. Gosens T, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. *Am J Sports Med*. 2011;39:1200-1208.
9. Jones EA, Kinsey SE, English A, et al. Isolation and characterization of bone marrow multipotential mesenchymal progenitor cells. *Arthritis Rheum*. 2002;46:3349-3360.
10. Laudy AB, Bakker EW, Rekers M, Moen MH. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. *Br J Sports Med*. 2015;49:657-672.
11. Murray IR, Geeslin AG, Goudie EB, Petrigliano FA, LaPrade RF. Minimum Information for Studies Evaluating Biologics in Orthopaedics (MIBO): platelet-rich plasma and mesenchymal stem cells. *J Bone Joint Surg Am*. 2017;99:809-819.
12. Peerbooms JC, Sluimer J, Bruijn DJ, Gosens T. Positive effect of an autologous platelet concentrate in lateral epicondylitis in a double-blind randomized controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. *Am J Sports Med*. 2010;38:255-262.
13. Piuzzi NS, Mantripragada VP, Kwee E, et al. Bone marrow–derived cellular therapies in orthopaedics: part II: recommendations for reporting the quality of bone marrow-derived cell populations. *JBJS Rev*. 2018;6:e5.
14. Rodeo SA. Biologic approaches in sports medicine: potential, perils, and paths forward. *Am J Sports Med*. 2016;44:1657-1659.
15. Rodeo SA. Moving toward responsible use of biologics in sports medicine. *Am J Sports Med*. 2018;46:1797-1799.