Editorial

Stem Cell Therapy for Knee Pain—What Exactly Are We Injecting, and Why?

Few developments in orthopaedic surgery have been accompanied by as much hype as the use of "stem cells." While the potential benefits of allogenic tissue-specific cells, stem cells, and progenitor cells are commonly discussed[1], and many clinical trials seem to be underway[2], few cell preparations have made their way through formal regulatory review and into orthopaedic practice.

It is difficult to clearly define the rules for the clinical evaluation of cell products within the regulatory environment, especially in the United States. Focusing just on cell preparations potentially available for cartilage repair, based on draft guidelines from the FDA (U.S. Food and Drug Administration) and the 361 exemption for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)[3], the processing of minimally manipulated cells of structural tissues must preserve the original relevant characteristics of the tissue relative to reconstruction, repair, or replacement; must be intended for homologous use only (e.g., use of musculoskeletal cells for musculoskeletal restoration); and may not be combined with another article (e.g., scaffold or carrier). The preparation may not have a systemic effect and must not be dependent on metabolic activity of living cells for its primary function, or else, for all practical purposes, it must be autologous. The relevant biological characteristics of cells of structural tissues (bone and cartilage) or nonstructural tissues (bone marrow or fat) generally include differentiation, proliferation, and/or metabolic activity, and "processing that alters any relevant biological characteristics of cells or nonstructural tissues generally would be considered more than minimal manipulation."[3] In vitro culture expansion would certainly be considered more than minimal manipulation. All other approaches to cell therapy currently require development under U.S. regulations of a premarket approval (PMA) or biological license application (BLA). An additional consideration is that, given the long-standing clinical practices of transplantation of autologous bone, cartilage, bone marrow, and periosteum, and based on the clinical premise of local cell repopulation, one might argue that many forms of autologous cell therapy, with and without the combination of other scaffold materials, are already well established. However, these practices have generally not been subjected to rigorous prospective trials.

In spite of the above regulatory considerations, mass advertising (Fig. 1) as well as an Internet search reveal the current clinical use of many cell preparations in orthopaedics, including for knee pain. Also among the more creative interpretations of "minimal manipulation" and "homologous use" related to the 361 HCT/P classification is the use of amniotic fluid and/or amniotic cell injections[4]. For example, according to 1 manufacturer[5], the product "is a cryopreserved, injectable amniotic fluid-derived allograft that is used to protect and promote development of the injured site. These human cells, tissues, and cellular and tissue-based products (HCT/Ps) are minimally manipulated amniotic fluid products and intended for homologous use only."[5] The interpretation that a natural role for amniotic cells is "wound-healing," and that cartilage repair as a type of wound-healing represents homologous use of amniotic cells, is indeed imaginative extrapolation.

In this issue of *The Journal of Bone & Joint Surgery,* Chahla and co-authors[6] present a systematic review of intra-articular cell therapies for osteoarthritis and focal cartilage defects of the knee. After screening 420 published titles and performing a detailed review of 34 articles, the authors could identify only 6 studies (4 Level II and 2 Level III) that met their criteria for inclusion. Unfortunately, the cell source, collection technique, cell processing methods, and method of delivery varied so widely that few conclusions were possible. For example, 2 studies used mixed autologous adipose-derived nucleated cells, 1 used mixed autologous blood-derived nucleated cells, and 3 used culture-expanded cells from bone marrow aspirations (2 autologous, 1 allogenic). Five of the 6 studies supplemented the cell injection with carriers (either platelet-rich plasma or hyaluronic acid), and only 1 study characterized

Fig. 1

Billboard advertisement seen near O'Hare International Airport in Chicago, June 30, 2016.

the number of progenitor cells being transplanted with a colony-forming unit assay. Although the studies generally reported favorable clinical outcomes and no major adverse events, the differences between study and control groups were modest and could be due to the placebo effect.

It is disappointing that so few high-quality clinical studies have been published, yet clinical applications of cell preparations seem to be forging ahead anyway. Chahla and coauthors appropriately emphasize that future studies should (1) use standardized nomenclature to describe the cell populations; (2) use objective characterization of the harvest site, methods, and cell population; (3) adequately describe the methods and effects of cell processing; (4) quantitatively report the composition of injected cells; (5) use standardized patient-reported outcome measures of pain and function before and after treatment; and (6) use high-quality imaging or other means of assessing structural outcome. Adoption of these guidelines should help us to recognize factors critical to the success of cell therapy and facilitate reviews of this type in the future. Although the Chahla review identified few reported complications so far, other case reports of neoplasm-like lesions arising at the site of stem cell therapy are worrisome[7-9]. As a community of clinicians, scientists, and regulators, we have a gap to fill in defining the parameters needed to promote both transparency and rigor in autologous and allogenic cell therapy, and we encourage publication of clinical studies, including those with "negative results," prior to widespread adoption of cell injection procedures. ■

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References

1. Diederichs S, Shine KM, Tuan RS. The promise and challenges of stem cell-based therapies for skeletal diseases: stem cell applications in skeletal medicine: potential, cell sources and characteristics, and challenges of clinical translation. Bioessays. 2013 Mar;35(3):220-30. Epub 2012 Sep 5.

2. ClinicalTrials.gov. Search results for "stem cells" and "arthritis". https://clinicaltrials.gov/ct2/results?term=%22stem+cells%22+and+%22arthritis%22&Search=Search. Accessed 2016 Jul 13.

3. U.S. Food and Drug Administration. Minimal manipulation of human cells, tissues, and cellular and tissue-based products: draft guidance. http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm427692.htm. Accessed 2016 Jul 13.

4. R3 Stem Cell. Amnion derived stem cell activatoe injections – from birth comes life. https://r3stemcell.com/stem-cells-treatments/amniotic-derived-stem-cell-injections/. Accessed 2016 Jul 13.

5. Applied Biologics. Flōgraft® – amniotic fluid-derived allograft. http://www.appliedbiologics.com/product-showcase/flograft/. Accessed 2016 Jul 13.

6. Chahla J, Piuzzi NS, Mitchell JJ, Dean CS, Pascual-Garrido C, LaPrade RF, Muschler GF. Intra-articular cell therapy injection for knee osteoarthritis and focal cartilage defects: a systematic review of the literature and study quality analysis. J Bone Joint Surg Am. 2016 Sept 21;98(18):1511-21.

7. Berkowitz AL, Miller MB, Mir SA, Cagney D, Chavakula V, Guleria I, Aizer A, Ligon KL, Chi JH. Glioproliferative lesion of the spinal cord as a complication of "stem-cell tourism". N Engl J Med. 2016 Jun 22. [Epub ahead of print].

8. Thirabanjasak D, Tantiwongse K, Thorner PS. Angiomyeloproliferative lesions following autologous stem cell therapy. J Am Soc Nephrol. 2010 Jul;21(7):1218-22. Epub 2010 Jun 17.

9. Amariglio N, Hirshberg A, Scheithauer BW, Cohen Y, Loewenthal R, Trakhtenbrot L, Paz N, Koren-Michowitz M, Waldman D, Leider-Trejo L, Toren A, Constantini S, Rechavi G. Donor-derived brain tumor following neural stem cell transplantation in an ataxia telangiectasia patient. PLoS Med. 2009 Feb 17;6(2):e1000029.