Editorial Commentary: Peripheral Blood Stem Cells Mobilization Using Granulocyte Colony-Stimulating Factor for Articular Cartilage Injuries: Wake Them Up and Make Them Come to You!

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Abstract: Articular cartilage injuries constitute a prevalent musculoskeletal problem in the general population. Restorative cartilage procedures are specifically challenging, as recapitulating hyaline cartilage can be difficult, thus compromising clinical outcomes. Progenitor cells for the treatment of articular cartilage injuries constitute a promising therapeutic method that has been increasing exponentially. Progenitor cells can be obtained from many different human tissues, such as bone marrow, adipose tissue, and muscle, as well as from peripheral blood after mobilizing stem cells from bone marrow with granulocyte colony-stimulating factor simulation. The minimally invasiveness, low complication rate, and efficacy of peripheral blood stem cells has gained significant attention and rapidly has become a promising source of progenitor cell delivery in the past decade.

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Cartilage injuries continue to be an important and common musculoskeletal problem in orthopaedic practices, where different treatment alternatives have been introduced in the past 50 years. The low intrinsic healing potential of cartilage tissue and the less-than-optimal fibrocartilage tissue obtained from several treatment options[1,2] are the main limitations in achieving near-normal cartilage tissue after repair procedures.

Despite the promising results[3-6] of current cartilage treatments, the ideal intervention is still a source of debate. This speaks to the lack of superiority among cartilage restoration treatments. When using adult chondrocytes, there are some concerns about their cell proliferation and differentiation capacity, as is the case with autologous chondrocyte implantation.[7] These issues have pushed clinicians and basic scientists to search for different treatment alternatives and cell sources that might be pluripotent in nature.

Although there are many issues that are still highly debated and over which there is no consensus, from the in vivo behavior to the way of its isolation and administration, and even to the mechanism of action and nomenclature, progenitor cells have already taken their place on the stage as the mysterious rock star of cartilage treatment because of their "potential" to differentiate into the native tissue. Following Arnold Kaplan's statement,[8] "they work, so use them," with "why not?" clinicians have increasingly shown their motivation for the use of these cells in cartilage treatments in recent years. Furthermore, the use of cell-based therapies in the treatment of musculoskeletal pathologies has increased exponentially in the past decade.[9]

According to the pericyte theory,[10,11] progenitor cells can be obtained from almost any human tissue. As such, progenitor cells are obtained from a variety of tissues, such as bone marrow, adipose, muscle, and peripheral blood.[12,13] In this regard, progenitor cells obtained from peripheral blood are less invasive to obtain compared with bone marrow–derived cells and have a similar chondrogenic differentiation potential.[14]

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The authors report the following potential conflicts of interest or sources of funding: J.C. reports other from Arthrex, ConMed Linvatec, Ossur, and Smith & Nephew, outside the submitted work; and board or committee member: American Orthopaedic Society for Sports Medicine; Arthroscopy Association of North America; and International Society of Arthroscopy, Knee Surgery, and Orthopaedic Sports Medicine: board or committee member. Full ICMJE author disclosure forms are available for this article online, as supplementary material.

0749-8063/21375/$36.00

https://doi.org/10.1016/j.arthro.2021.03.026

Peripheral blood stem cells (PBSCs) are based on the concept of mobilizing stem cells from the bone marrow with the administration of granulocyte colony-stimulating factor and collecting them from peripheral blood that is commonly used in other medical fields. PBSC technology has gradually increased since its first in vivo study[15] in 2004, demonstrating promising results.[16]

We read the recent study by Saw, Anz, Ng, Jee, Low, Dorvault, and Johnson[17] titled "Arthroscopic Subchondral Drilling Followed by Injection of Peripheral Blood Stem Cells and Hyaluronic Acid Showed Improved Outcome Compared to Hyaluronic Acid and Physiotherapy for Massive Knee Chondral Defects: A Randomized Controlled Trial" with great interest. We thank the authors for their elegantly executed study seeking to compare the effectiveness of PBSC plus hyaluronic acid after arthroscopic subchondral drilling with hyaluronic acid plus physiotherapy (control group) in a dual-center, randomized controlled trial for massive chondral defects of the knee joint. Randomized controlled trials in the biologic arena are scarce and, thus, we commend the authors in performing high-quality research in this field.

An important area in biologics is standardization in the reporting of cell-based treatments. To this point, the DOSES consensus outlined characteristics that needed to be reported to achieve maximal transparency as well as external validity of the studies involving progenitor cells.[18] Saw et al.[17,19-22] should be commended for continuing their line of research since 2005 regarding the effectiveness of PBSCs for the treatment of chondral injuries, as it has helped build on this novel concept consistently. In their previous studies, the authors reported that an 8-mL injection of fresh PBSCs on the seventh postoperative day contains an average of 20 million CD105+ cells. They also reported that the repair tissue obtained after PBSC treatment had hyaline cartilage histologic features.[20,21] Second-look arthroscopic biopsy data containing detailed information about the microstructural features of the repair tissue within this large patient group would be beneficial.

A dose-dependent response of granulocyte colony-stimulating factor has been reported long before its use in orthopaedic practice, and its possible side effects are widely available in the literature.[23] Although the authors seem to have opted for a safe range by choosing a low dose, there are differences between the dose−response data reported previously[24] and the stem cell counts obtained in the current study. Randomized clinical trials with different cell dosage, with specific attention to the side effect profile, will further contribute to the delineation of the ideal treatment protocol. Unlike their previous study published in 2013,[21] diagnostic arthroscopy and microfracture were not performed in the control group in this current study. Performing the same surgical procedure on the control group would better demonstrate the isolated effect of PBSC independent of the microfracture procedure.

Of note, one important limitation to this procedure is ensuring patient compliance with the treatment, which includes 14 knee injections over the course of 18 months.[25] In addition, storage conditions, cost, and reduced cell viability in cryopreserved applications also can be listed as other concerns for the long treatment protocol.

It is also interesting that the study successfully visualized the microfracture holes and the cartilage tissue formed around them. The presented images in the recent study reveal the effect of the depth of microfracture holes and the distance between them on the treatment results and why we need novel microfracture methods. However, images of cartilage repair tissue formed only around the microfracture site can lead to believe that the scaffolding capacity of fibrin clots that forms in the microfracture defect area might not be ideal (as it has been previously reported[26] in lesions over 2 cm^2). Thus, this might not create an optimal microenvironment in massive chondral injuries for a homogeneous distribution and proliferation of cells.

In conclusion, we congratulate the authors for their line of research on PBSCs and their recent well-designed randomized clinical study. International collaborations along with well-designed studies will allow us to advance the field. To this point, we encourage them to continue to further develop this concept as an alternative of cartilage repair.

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