PM R 10 (2018) 524-532

www.pmrjournal.org

Point/Counterpoint

Guest Discussants: Gerard A. Malanga, MD, Samuel Dona, MD, Joanne Borg-Stein, MD, Michael Auriemma, MD
Feature Editor: Jaspal R. Singh, MD

Refractory Knee Osteoarthritis: Adipose-Derived Stromal Cells Versus Bone Marrow Aspiration Concentrate

CASE SCENARIO

A 56-year-old woman presents to the clinic with a long history of right knee pain. The pain began insidiously 4 years prior and she reports a slow progression in pain and decrease in her function. She has been treated with oral analgesics and anti-inflammatories. In addition, she is currently enrolled in her third round of physical therapy. Last year she had an intra-articular corticosteroid injection, which gave her about 6 weeks of relief. Following this, she underwent a series of 3 hyaluronic acid injections (SupartzFX) that she completed 3 months ago. She reports that this injection did not provide her with significant relief. The patient reports primarily knee pain over the medial joint line. Her alignment is normal and she does not report any swelling, buckling, or locking of her knee. The pain is worse when going up and down stairs, but she does not report any falls. Radiographs and magnetic resonance imaging (MRI) of the right knee reveal moderate to severe tibiofemoral osteoarthritis (Kellen Lawrence grade 3) with mild medial meniscus fraying. There is no discrete meniscus tear, and the anterior and posterior cruciate, and medial and lateral collateral, ligaments are intact.

She was reading information on the role of "stem cells" injected into the knee that could regenerate and repair her degeneration. Drs Gerald Malanga and Samuel Dona will argue for adipose-derived stromal cells (ADSCs). Drs Joanne Borg-Stein and Michael Auriemma will argue for bone marrow aspiration concentrate (BMAC).

Drs Malanga and Dona Respond

This case scenario of a young woman with a history of knee osteoarthritis (OA) is typical and commonly seen in primary care, physiatric, and orthopedic offices around the world. Many patients continue to suffer with pain after completing the various available nonoperative interventions that comprise the traditional treatment algorithm of degenerative knee OA, including oral medications, physical therapy, bracing, corticosteroids, and hyaluronic acid injections. The long-term efficacy of these therapies is poor [1], often resulting in many years of progressive pain and loss of function for those who decline or are not deemed appropriate candidates for surgery. London et al define this period as the "osteoarthritis treatment gap" [2]. This is defined as the "time from unsuccessful exhaustion of conservative measures to surgical intervention." In addition to compromising physical capabilities and negatively impacting quality of life, London et al has noted the economic consequences of patients who fall into this treatment gap of knee OA management. More than 27 million middle-aged and older adults in the United States share this situation today [3]. The prevalence of knee OA is projected to increase with rising obesity rates and the continued aging of our population. There are approximately 700,000 TKAs performed annually at this time, and the fastest-rising incidence is occurring between 40 and 50 years of age [4]. Among countless others, this patient is now faced with limited choices in the management of her knee pain. It is therefore important that nonoperative specialists develop and trial innovative treatment methods to successfully bridge this treatment gap to maintain function and ease the financial burden of these patients.

1934-1482/$ - see front matter
https://doi.org/10.1016/j.pmrj.2018.03.021

The potential for regenerative medicine to fill this role has gained considerable interest in recent literature and clinical practice. These treatments are often lumped into a category described by our patients and the media as "stem cell" therapy. The term *orthobiologic treatments* is perhaps a better designation and includes platelet-rich plasma, autologous bone-marrow concentrate (BMAC) and adipose-derived mesenchymal stem cell therapies. When applying the label "stem cells," there is relevant terminology that is frequently used improperly. Mesenchymal stem cells (MSCs) have been defined as multipotent adult stem cells that self-renew and have the ability to differentiate into various cell types, that is, muscle, bone, cartilage, etc [5]. These cells can be obtained from a patient and subsequently injected into a site of injury in the same patient (ie, autologous use). MSCs also reveal paracrine activity by releasing various growth factors and exhibit immunomodulatory capability [5].

For the purposes of this point/counterpoint, we will refer to adipose regenerative therapy as adipose-derived "stromal" cells (ADSCs) instead of adipose-derived "stem" cells. ADSCs are MSCs that have been isolated from homogenized adipose tissue located in the capillary and perivascular adventitia of large blood vessels within adipose tissue. Bone marrow—derived mesenchymal stem cells (BMSCs) are isolated from bone marrow aspirate (BMA) or bone marrow aspirate concentrate (BMAC) harvested from the trabeculae of marrow cavities. ADSCs and BMSCs are both felt to have a pericyte origin, with the same ability to express common cell surface markers, gene expression profiles, and differentiation potential [5]. Although ADSCs share common characteristics in morphology and phenotype with BMAC, recent literature has shown several distinct differences between these 2 alternative stem cell sources [6].

Compared with BMAC, studies have noted ADSCs are present in higher numbers per unit volume of tissue, more rapidly proliferate in culture, and are less susceptible to senescence secondary to culture expansion (see summary by Malanga and Ibrahim [5]). Furthermore, these studies revealed considerable variability in MSC concentration between ADSCs and BMAC. A gram of adipose tissue yields approximately 2 x 106 nucleated cells, with an estimated 5% being ADSCs, as compared to 1 mL of bone marrow aspirate yielding close to 6 x 106 cells, with roughly 0.01% of these representing true mesenchymal stem cells [6]. ADSCs may have a higher yield of cell counts between these MSC-based therapies, and therefore a potentially better strategy for knee OA.

Although ADSC therapies appear to be a beneficial treatment option for patients with knee OA, the Food and Drug Administration (FDA) continues to be concerned about the appropriate use of all stem cell therapies and especially those derived from adipose tissue. A recently published guideline [7] has stressed the importance of several areas for practitioners to be compliant in the use of these cells. Of first importance is the autologous use of ADSCs, which entails that all individuals undergoing therapy serve as both the donor and recipient, with strict regulation that includes same-day, nonexpanded use of harvested cells. Additionally, FDA criteria state that the use of adipose tissue must meet "minimal manipulation," which is defined as "processing of the human cells, tissues, and cellular and tissue-based product (HCT/P) that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement." The FDA considers adipose tissue to be a structural tissue in this regard for application of the regulatory framework and processing should not alter the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support. The FDA further specifies that the relevant characteristics of adipose tissue relate to its ability to provide cushioning and support because of its bulk and lipid storage capacity. The FDA expresses reservations that the manufacturer processes adipose tissue by removing the cells (such as after enzymatic digestion), leaving the decellularized extracellular matrix portion. This would generally be considered more than minimally manipulated because this processing alters the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support. Likewise, the FDA states that the HCT/P must be meant for "homologous use," meaning that "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P must perform the same basic function or functions in the recipient as in the donor." Currently, there are FDA cleared devices for the harvesting, concentrating, and transferring of autologous adipose tissue for musculoskeletal applications. These devices incorporate "sizing and washing" technology that have been defined by the FDA to preserve the cell and tissue microarchitecture of the adipose tissue, eliminate residues of oil emulsion and blood, and provide a tissue that is minimally manipulated in accordance with the FDA guidelines.

A comprehensive review of the literature regarding the use of regenerative medicine options in knee OA historically reveals a greater amount of publications related to the study and clinical human application of BMAC. However, in the past 5 years there has been increasing evidence in research supporting the positive effects of ADSCs on improving knee joint pain and function. These studies have shown a positive effect on the progression of knee OA by reducing articular damage and cartilage degeneration [8-10]. Pagani et al performed an in vitro comparison study between BMAC and ADSCs in various inflammatory microenvironments to determine any differences in chondrogenesis [11]. Although both BMAC and ADSCs developed into mature micromasses, the ADSCs had increased matrix