Perspective

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Osteoarthritis: From Platelets to Mesenchymal Stem Cells

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Introduction

The range of biological agents to treat osteoarthritis is in constant expansion, and recent trials suggest that amnion-derived products (such as umbilical cord stem cells or amniotic allograft suspension) may provide significant symptomatic relief and functional improvement compared with traditional injectables [1]. Anyway, in many countries, stringent limitations exist on the manipulation and homologous use of placenta-derived products, and therefore, collecting more data is mandatory to endorse their use for musculoskeletal diseases in a safe and clearly regulated way. More in general, an increasing interest toward orthobiology has been observed in recent years, which led to the introduction in clinical practice of many minimally invasive strategies to treat osteoarthritis, from platelet-rich plasma to mesenchymal stem cells. On the basis of this trend, which involves physicians from different specialties, it would be fundamental to have clear guidelines establishing the correct use of these products in the setting of clinical routine not only to safely provide patients the most advanced therapeutic options but also to protect our practice from potential legal issues.

Description

The increasing application of biological products in orthopaedics has introduced something unexpected in our clinical practice: Whereas a couple of decades ago, our activities were more on the "metal side" of the job (arthroplasty) [2], now many of us have taken confidence with "unconventional" orthopaedic procedures or devices, such as bone marrow harvesting, lipoaspiration, platelet-rich products, collagen membranes, and coral-based scaffolds. Nobody at the beginning of 2000 would have ever imagined taking care of osteoarthritis (OA) by processing autologous fat after a liposuction from the patient's abdomen [3]. Although someone might regret the old times when hammering an acetabular component was one of the supreme efforts of orthopaedic strength, things have now changed and we face more subtle challenges, such as the choice of the right injectable to treat our OA patients and the list is quite long8! Some individuals (usually "old-school guys") may argue that we are becoming some sort of chemists using strange biological products to temporarily reduce pain. Others (the "bad guys") may even argue that all this stuff is just a commercial hype with the aim of making money with fashionable products whose efficacy has not been fully proved [4]. We instead prefer a more "literary" approach and think that we are acting as a sort of modern "alchemist" (which also sounds more attractive than simple chemists . . .), dedicated to discovering our philosophers' stone, that is, the cure for OA.

Beyond any joke and beyond any negative prejudice toward alchemists, if we look more carefully at history, we will find that many famous alchemists were actually polymaths and precursors of modern science. It is not fiction that Isaac Newton (just to cite one big name) was interested in alchemy and wrote on that topic for most of his life. Alchemy was regarded as the converging point of different disciplines; similarly, "orthobiology" is the result of the integration of different areas of research, starting from biology and biomechanics, passing through biomaterials engineering, and finally reaching clinical application [5]. This complex process has led to the introduction of

therapeutic options for cartilage defects and OA over the past few decades, such as chondrocyte transplantation, platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), and osteochondral scaffolds.

Here emerges a clear difference with the mythological philosophers' stone, whose purpose, as we all know, was to transform base metals into gold: in our field there are already too many practitioners able to turn joints into "metallic" entities, so the real orthopaedic stone is something able to delay or prevent joint replacement. In their article titled "Safety and Efficacy of an Amniotic Suspension Allograft Injection Over 12 Months in a Single-Blinded, Randomized Controlled Trial for Symptomatic Osteoarthritis of the Knee," Gomoll, Farr, Cole, Flanigan, Lattermann, Mandelbaum, Strickland, Zaslav, Kimmerling, and Mowry16 describe the results of an amniotic suspension allograft (ASA) injection for the treatment of moderate knee OA. They performed a 3-arm randomized controlled trial comparing ASA with a single administration of hyaluronic acid or placebo. The article has many interesting points. First, it stimulated our curiosity toward placenta-derived products: after a brief research, we were amused to learn the disparate applications of the placenta in history, from its magical use in the Middle Ages to the medical field and to . . . "gastronomy" (although "placentophagia" has been the subject of studies,17 this time we prefer more traditional approaches!).

Looking at the results of the study by Gomoll the first thing we noticed was the lack of a significant difference between placebo and hyaluronic acid at the 12-month evaluation, with saline solution even performing better at the 6-month time point. This finding could be attributed perhaps to the specific hyaluronan used, but in any case, this is further proof that nothing should be taken for granted and that comparison to a placebo is always methodologically sound. The outcomes after the injection of ASA were superior to those of the other treatment groups, with a higher number of responders, as well as substantial stability of the results up to the final follow-up. ASA is a homologous product that contains amniotic particulate, amniotic cells, and a milieu of other bioactive agents, such as growth factors and cytokines, that synergistically contribute to restore joint homeostasis, which is the crucial mechanism of action of biological products. In fact, "cartilage regeneration," although attractive as a concept, is still far from being achieved, and recent high-quality literature has shown that biological agents act mainly on the joint environment by reducing catabolic and inflammatory distress, thus protecting joint tissues from further damage. This is translated into pain improvement and restored function for patients, as shown by the present trial.

Apart from the encouraging results described, the use of amnion-based products warrants some considerations in terms of regulatory issues because in most countries, "private banking" of placentas is still forbidden, and the manipulation of these tissues is strictly regulated, with a limited range of clinical applications currently allowed (and OA is usually not among those). Furthermore, other trials have been investigating the role of cultured, umbilical cord–derived MSCs in OA, thus confirming the great interest toward this source of biological agents. Further randomized trials will help in confirming the safety profile, the correct therapeutic indication, and the efficacy of placenta-derived products with the goal of introducing them, in a safe and regulated way, as a treatment option for a wider segment of patients. What has clearly emerged from recent literature is that orthobiology is no more a marginal field in musculoskeletal medicine and no more a territory dominated by basic researchers; conversely, it is now constantly attracting a larger number of clinicians, from different specialties.

Conclusion

On previous occasions, we have advocated that any biological agent should not be used in routine clinical practice until a solid amount of data has been released on its efficacy. This is to avoid any indiscriminate use that does not help the medical community and may even be harmful for patients. We still strongly believe in this statement, but we must also acknowledge that most orthopaedic practitioners are "careful" users of those products; therefore, if sound research is necessary to endorse routine application, then routine application must be constantly supported by science. This means that scientific publications should protect our everyday practice and legitimate our choices. Many of us are currently using PRP or MSCs from various sources as minimally invasive treatments for OA with the aim of delaying more invasive approaches in young patients or in patients affected by significant comorbidities. We are doing this because, in recent years, some relevant evidence has emerged on the safety and efficacy of these products, especially PRP, which many recent meta-analyses have proved to be superior to viscosupplementation. To this purpose, it is worth underlining that the guidelines of many international societies do not consider biological injections for knee OA at all-or even recommend against their use. This is the case for the American Academy

of Orthopaedic Surgeons, whose guidelines state that "inconclusive evidence" exists on the role of biologics. Osteoarthritis Research Society International guidelines do not even discuss the role of biologics, limiting the choice to only corticosteroids and hyaluronate. The American College of Rheumatology instead "strongly" recommends against the use of PRP or MSCs in hip and knee OA, whereas they only recommend against the use of prolotherapy and intra-articular botulinum toxin, which are not exactly the most common therapeutic treatments used by most orthopaedic practitioners.

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