ORTHOBIOLOGICS

TARGET OSTEOARTHRITIS

– Written by Angelo Boffa, Stefano Zaffagnini, and Giuseppe Filardo, Italy

INTRODUCTION

Osteoarthritis (OA) is a common disease characterized by progressive deterioration and loss of articular cartilage with concomitant structural and functional changes in the entire joint, involving synovium, meniscus, periarticular ligaments, and subchondral bone. OA affects more than 10% of the world population aged 60 years or older and represents one of the major causes of disability worldwide, with a massive impact on society both in terms of quality of life for the individuals and high costs for the healthcare systems. Clinical features of OA are mostly characterized by signs and symptoms of inflammation, including pain, effusions, and loss of mobility, often associated with significant functional impairment and disability.

Current strategies to manage OA include weight loss, physical treatments, oral medications such as non-steroidal anti-inflammatory drugs and acetaminophen, and intra-articular injection therapies with corticosteroids and hyaluronic acid (HA). These conservative therapies have modest and short-lasting efficacy and are not able to arrest the underlying disease process. Thus, the final treatment is often represented by joint replacement, which is invasive and not free from complications, especially in young and active patients. In this light, research efforts have been made to find new minimally invasive and potentially disease-modifying procedures to address patients with OA in order to delay or avoid surgery. Among these, orthobiologics are gaining increasing interest due to the availability of several promising products with a biologic potential in improving joint tissues healing, ranging from platelet concentrates to minimally manipulated mesenchymal stromal cells (MSCs) obtained from bone marrow or adipose tissue. The evidence for these approaches derives largely from their intra-articular applications to address degenerative joint disease, in particular for knee OA.

This article will describe rationale and clinical evidence of the most used orthobiologics for the management of OA.

RATIONALE

The use of orthobiologic injectables is growing in the clinical practice with the aim to reduce symptoms, restore a satisfactory joint function, and possibly prevent OA progression delaying the need for surgery. These approaches exploit the high concentrations of growth factors, cytokines, and bioactive molecules of blood derivatives, as well as the presence of mesenchymal stromal cells (MSCs) in tissue derived concentrates.

- Platelet Rich Plasma (PRP) has gained increasing attention due to the high concentration of bioactive molecules stored in platelet α-granules, which showed to take part in the homeostasis of joint tissues, being involved in both healing process and immunoregulation. These biologically active proteins seem to be able to promote a positive joint environment, favoring the restoration of a homeostatic balance in OA joints. PRP showed different and heterogeneous mechanisms of action, including the increase of chondrocyte proliferation rate, matrix production stimulation, and inflammation modulation. PRP may also significantly enhance synoviocyte HA secretion and switch synovial angiogenesis to a more balanced status, as well as increase the expression of biglycan and decorin in meniscal cells. Pre-clinical evidence further supports the role of PRP in modulating the intra-articular environment by counteracting inflammation in degenerative joint diseases. PRP injections showed disease-modifying effects in experimental animal studies, attenuating the progression of cartilage tissue damage and reducing the inflammatory reaction of the synovial membrane in OA joints[1].

- Bone Marrow Aspirate Concentrate (BMAC) has been proposed as a promising option for the treatment of cartilage lesions and OA, being a combination of biologically active proteins and cells obtained through a mini-invasive and technically easy procedure. The rationale for the use of BMAC relies on the transplantation of the entire bone marrow niche which contains MSCs, hematopoietic precursors, monocytes, and endothelial cells, as well as a great array of soluble factors. All these are involved in several pathways crucial for cell maintenance and function, differentiation, extracellular matrix production, and for the regulation of cell catabolic/anabolic activities. Bone marrow MSCs showed the ability to differentiate toward several lineages (i.e., chondrocytes, osteoblasts) and to produce growth factors, which may positively affect joint homeostasis and eventually contribute to relief pain and to improve joint function[2]. Accordingly, this combination of cells and bioactive proteins makes BMAC a unique product among currently available orthobiologics, with the rationale of potentially altering OA course.
- Adipose-derived products have been recently proposed as promising alternatives for the management of OA, thanks to the advantages provided by adipose tissue over other MSCs sources. In fact, adipose tissue is easily accessible, abundant, and obtainable with a mini-invasive procedure offering a high number of cells and pericytes (MSCs precursors). Adipose tissue contains approximately 500–2500 times more MSCs compared to the same volume of bone marrow[3]. Moreover, while the number of MSCs contained in bone marrow decreases with age, the available in the adipose tissue is quite stable during life, representing an aspect that is very beneficial for an elderly population[4]. Adipose tissue can be processed at the point of care into cell suspensions, producing the Stromal Vascular Fraction (SFV), or as microfragments, producing the Micro Fragmented Adipose Tissue (MF-AT). Compared with bone marrow-derived MSCs, adipose-derived MSCs showed to be more genetically stable, with higher proliferative and differentiation capacity, longer telomere length, and lower senescence ratio[5].

CLINICAL EVIDENCE

Platelet Rich Plasma (PRP)

PRP is gaining a large interest in the clinical practice as a minimally invasive injective OA treatment thanks to its safety, low costs, and simple preparation technique to obtain its biologically active content (Figure 1). Since the first clinical applications, several studies supported the safety and effectiveness of PRP for the treatment of knee OA, demonstrating satisfactory results in terms of reduction of pain-related symptoms and functional improvement up to 12 months. These benefits have been observed especially in young patients and early OA stages. Despite the large placebo effect ascribed to intra-articular injections, in particular when dealing with new products such as PRP, a recent meta-analysis on 34 randomized controlled trials (RCTs) showed that PRP injections provided a statistically and clinically significant improvement in patients with knee OA compared to saline injections at 6 and 12 months of follow-up, without increasing the risk of adverse events[6]. Moreover, PRP injections provided better clinical results than other commonly used injective strategies such as corticosteroids or HA at 6 and 12 months of follow-up[6]. Some studies suggest that the clinical improvement provided by PRP can be perceived by patients also beyond 24 months, with a subsequent gradual reduction over time[7]. A recent retrospective study and survival analysis also showed that PRP may delay the need for total knee arthroplasty (TKA) with a median of 4 years and with a survival rate of 85% at 5 years of follow-up[8].

Recently, some researchers investigated the effectiveness of subchondral injections of PRP to address patients with knee OA. Sànchez et al analyzed the combined

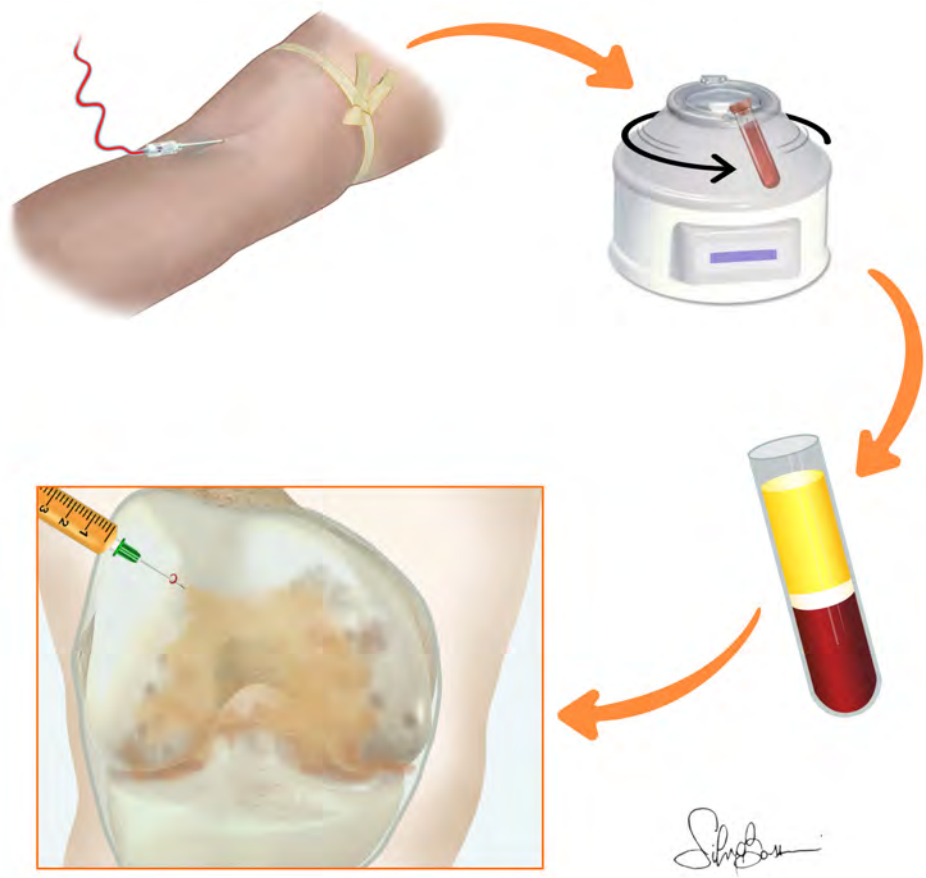

Figure 1: Peripheral venous blood is harvested from the patient arm and then processed using a centrifuge to separate the blood components obtaining three layers: erythrocytes (45% of whole blood), "buffy coat" (<1% of whole blood), and platelet poor plasma (PPP - 55% of whole blood). Erythrocytes and PPP are discharged to obtain the layer concentrated in platelets (with or without leukocytes) - PRP, which is injected into the knee.

use of subchondral and intra-articular PRP injections reporting the safety of this strategy, with rare and mild adverse events, and supporting its effectiveness in improving functional status and reducing pain, with a relatively low rate of conversion to TKA[9]. More recently, the same group observed better clinical results at 6 and 12 months in favor of the combination of subchondral and intra-articular PRP injections compared to intra-articular injections alone in 60 patients with a prevalent grade 3 knee OA according to the Ahlbäck scale, confirming the importance of directly targeting also the subchondral bone area[10]. The biological effects of subchondral PRP injections have been evaluated by Lychagin et al through the measurement of the levels of the serum cartilage oligomeric matrix protein (COMP), an early biomarker for the remodeling of articular cartilage, in OA patients treated with subchondral PRP injections[11]. They found a consistent increase of serum COMP levels after the procedure, which in the authors conclusions could reflect the effects on cartilage turnover resulting from the subchondral treatment.
Despite the promising clinical results, no consensus or guidelines still exist among the scientific societies of orthopedic surgeons, rheumatologists, and physiatrists, on the most suitable indications for the use of PRP in the treatment of OA. This is likely due to the relatively new evidence as well as the lack of a standardized protocol and to the wide availability of different PRP preparation methods. These can yield products with different composition and characteristics in terms of number of platelets and leukocytes, volume of whole blood harvested or PRP obtained, storage procedures, activation method of platelets, formation of a fibrin matrix, etc... Many questions remain open, and all this makes it very difficult to merge and analyze clinical results of different studies and to gain a full understanding of the real benefits of this biological approach. Further studies will have to investigate all these aspects to better understand the potential and limitations of PRP for the treatment of joints affected by OA.

Bone Marrow Aspirate Concentrate (BMAC)
BMAC has been widely applied in the clinical practice for the treatment of cartilage lesions first and, more recently, it has been proposed as a promising mini-invasive approach to treat degenerative orthopedic conditions like knee OA (Figure 2). Only a few pre-clinical studies analyzed the effects of BMAC injections to address OA joints. In vivo OA models reported that BMAC provided better results in terms of macroscopic, histological, radiological, and immunohistochemical findings compared with control groups (saline, HA, or PRP)[12]. The available clinical studies investigating the use of BMAC to address OA evaluated mainly the knee injective treatment, while only few studies focused on shoulder, hip, or ankle OA[12]. Despite an overall poor methodology and a significant heterogeneity, these preliminary trials reported promising results for OA in terms of safety and effectiveness for symptoms management of this intra-articular approach, which led to pain relief and knee function improvement. Nevertheless, the few comparative studies available in the literature did not show BMAC superiority over the other intra-articular options, and the only placebo-blinded RCT was not able to prove BMAC superiority over saline at 12 months of follow-up[13].

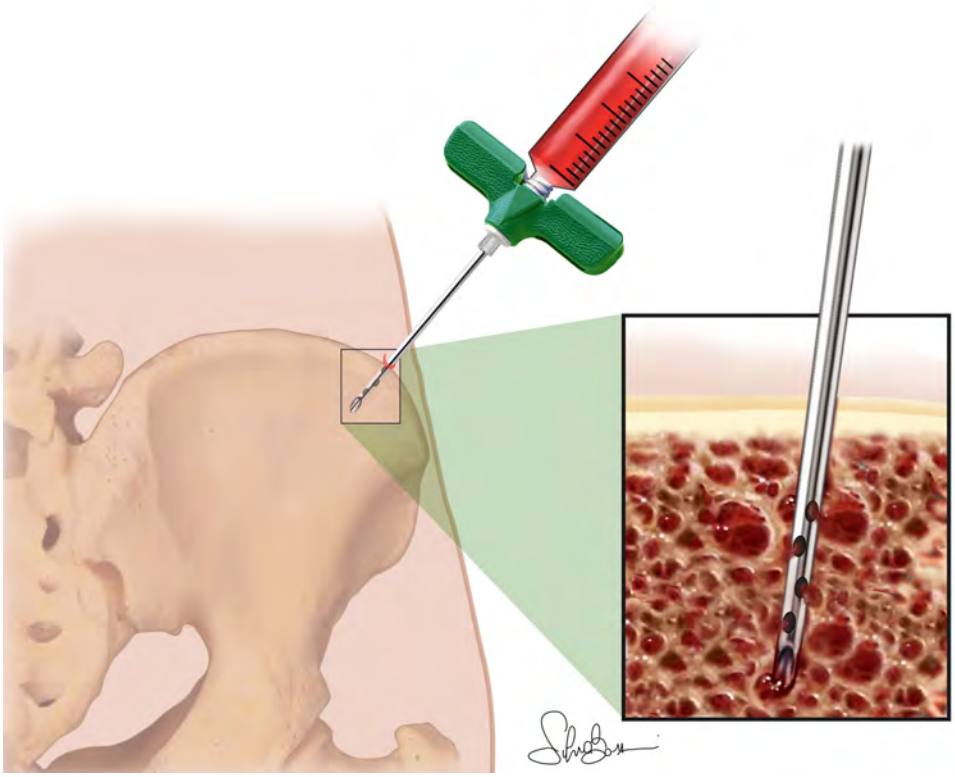

Figure 2: In a one-step technique the bone marrow is harvested from the iliac crest. The procedure is performed under spinal loco-regional anesthesia. The trocar is inserted and advanced, and bone marrow is harvested with a syringe coated with anticoagulants. The bone marrow aspirate is centrifuged to obtain the bone marrow aspirate concentrate (BMAC).

A new application of BMAC has been recently suggested to further exploit its potential by targeting the subchondral bone, which is commonly involved in the OA processes. The subchondral BMAC administration demonstrated promising clinical results in preliminary reports on knee OA. The first evidence has been reported in an RCT by Hernigou et al, which evaluated 30 young patients with bilateral knee OA secondary to osteonecrosis and treated with subchondral BMAC injections on one side, and with TKA on the other side. BMAC injections provided similar clinical outcomes compared with TKA, but a lower complication rate and a quicker recovery[14]. The same authors analyzed 140 patients with medial knee OA planned to undergo bilateral TKA and treated with subchondral BMAC injections on one side and with TKA on the other side. Subchondral BMAC injections provided an effect on pain that allowed to postpone or avoid TKA up to 15 years of follow-up, with only 25 patients requesting TKA in the knee treated with BMAC[15]. Hernigou et al also described the superiority of subchondral BMAC injections

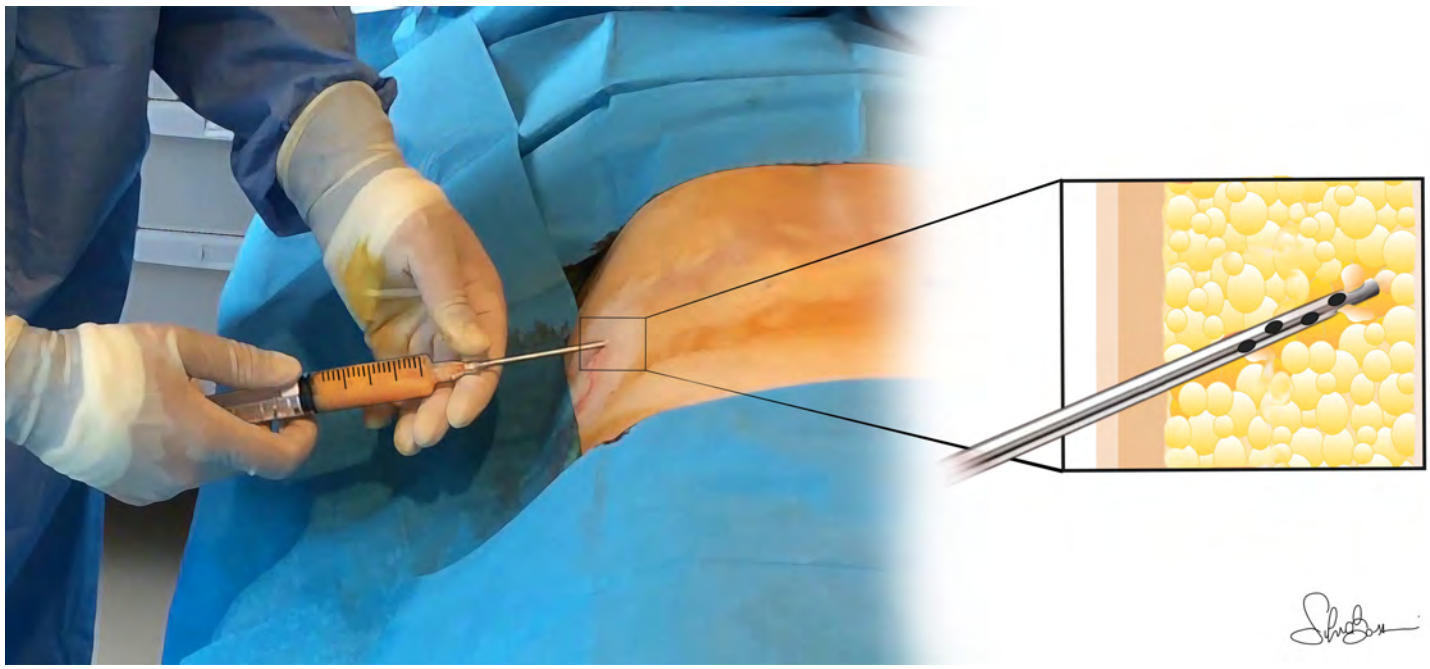

Figure 3: Adipose tissue is harvested from the subcutaneous abdominal fat (usually the lower or lateral abdomen). The site is injected with adrenaline and lidocaine and then the adipose tissue is collected with a blunt cannula. The harvested fat is immediately processed (mechanically or with enzymatic digestion, with or without centrifugation according to the specific procedure) for SVF or MF-AT one-step injection.

over intra-articular BMAC injections in an RCT on 60 patients with bilateral knee OA, showing in the subchondral group a lower yearly arthroplasty incidence (1.3% versus 4.6%) and higher clinical and magnetic resonance imaging (MRI) improvements at 2 years of follow-up[16]. A recent prospective multi-centric study of Kon et al evaluated the combined approach of subchondral and intra-articular BMAC injections to address 30 patients with symptomatic knee OA with associated subchondral bone alterations. The authors documented a significant clinical improvement up to 12 months of follow-up, while the MRI evaluation showed a reduction of bone marrow edema, suggesting that targeting with BMAC both subchondral bone and joint environment can provide promising results to treat knee OA[17].

Still, the application of BMAC to address patients with OA joints has a limited scientific support and more high-level studies are needed to understand if this product could represent a valid option among the different biological treatment strategies. Moreover, many aspects remain to be clarified to optimize the potential of BMAC, including methods of harvest and centrifugation, timing of injection, and application modality, and to provide a standardized method targeted to the OA treatment.

Adipose-derived products

Adipose tissue can be obtained with a minimally invasive procedure and processed at the point of care into cell suspensions, producing SVF or MF-AT (Figure 3). SVF is generally obtained with an enzymatic method, which consists of digesting the lipoaspirate with collagenase to break down the matrix and release MSCs and other cells. Subsequently, the collagenase is removed by dilution and washing, followed by centrifugation[18]. SVF application showed safety, feasibility, and effectiveness for the treatment of joints affected by degenerative cartilage lesions and OA in pre-clinical studies, improving of the quality of the cartilage with respect to control groups[18]. Several trials analyzed SVF injections in the clinical practice, reporting a low rate of adverse events and improvement in pain and functional outcome scores in patients with knee OA, although most studies are case series without a comparative arm[19]. A recent double-blind placebo-controlled RCT on 39 patients with knee OA showed a statistically significant improvement in the SVF group compared to the control group up to 12 months of follow-up, although MRI did not reveal changes in cartilage thickness after treatment[20]. Moreover, intra-articular SVF demonstrated better clinical and imaging findings at 12 months compared to HA in an RCT on 32 patients with knee OA[21]. Despite these promising findings, these studies analyzed only small sample sizes and thus further high-level studies are needed to clarify the real therapeutic potential of SVF.

MF-AT treatment is also gaining interest in clinical practice, since it is obtained through a simple, minimal mechanical manipulation that leads to a progressive reduction in the size of adipose tissue clusters with the elimination of oil and blood residue. MF-AT approach has the advantage of preserving cell integrity and tissue microarchitecture, providing a high number of cells and growth factors, without the need for enzymatic or expansion treatment[22]. The benefits of this products were observed in in vitro studies, reporting a better (qualitatively and quantitatively) secretion of growth factors and cytokines involved in tissue repair compared to the enzymatic methods[23]. Moreover, MF-AT contains a significantly higher concentration of exosomes secreted by MSCs compared to the enzymatic method, suggesting a better preservation of the paracrine potential of adipose MSCs and

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thus their efficacy[24]. To this regard, a recent in vivo pre-clinical study reported better results in terms of protection of the articular surface from the joint degenerative OA processes in rabbits treated with MF-AT compared to those treated with SVF or expanded adipose-derived MSCs[25]. MF-AT injections showed promising results also in the clinical practice in patients with knee OA, with a low number of adverse events and a significant improvement in pain, function, and quality of life[26,27]. Despite the growing number of clinical studies focusing on intra-articular MFAT injections for knee OA, high-level studies comparing the effectiveness of this product with other injectables are still limited. Therefore, further studies are needed to clarify the potential of MF-AT and the advantages versus other injective options to treat OA joints.

CONCLUSIONS

The management of OA remains an important challenge for physicians, and orthobiologic approaches can play a key role thanks to their potential in modulating the articular environment. Several products ranging from PRP to minimally manipulated MSCs strategies are frequently performed in patients with symptomatic OA, although their indications and guidelines are not always clear. Despite the increasing use in the clinical practice, evidence on these injective approaches is still limited and not able to guide clinicians in choosing the best product, indication, formulation, injections schedule, as well as many other aspects related to both products and patient management. Further research efforts are needed to define potential and limitations of each biological strategy for the conservative treatment of joints affected by OA.

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References

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Angelo Boffa M.D.
Doctor
Clinica Ortopedica e Traumatologica
IRCCS Istituto Ortopedico Rizzoli
Bologna, Italy

Stefano Zaffagnini M.D.
Professor
Director
Clinica Ortopedica e Traumatologica
IRCCS Istituto Ortopedico Rizzoli
Bologna, Italy

Giuseppe Filardo M.D., Ph.D.
Professor
Applied and Translational Research (ATR) center
IRCCS Istituto Ortopedico Rizzoli,
Bologna, Italy

Orthopaedic and Traumatology Unit,
Ospedale Regionale di Lugano, EOC

USI - Università della Svizzera Italiana,
Facoltà di Scienze Biomediche,
Lugano, Switzerland

Contact: angeloboffa@libero.it