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Review of Orthobiologics and The Osteoarthrosis Treatment Gap

Delesky EM[1], Jow S[2], Bowen J[3] and Malanga G[4]*

[1]Cooper Medical School of Rowan University, USA

[2]Physical Medicine and Rehabilitation, MedStar Georgetown University Hospital, USA

[3] Physical Medicine and Rehabilitation, Rutgers University, USA

[4]Physical Medicine and Rehabilitation, Rutgers University, USA

*Corresponding author: Dr. Malanga G, Physical Medicine and Rehabilitation, New Jersey Medical School, Rutgers University, Newark, NJ; New Jersey Regenerative Institute LLC, 197 Ridgedale Avenue, #210, Cedar Knolls, NJ 07929, United States. E-mail: gmalangamd@hotmail.com

Abstract: Patients with knee Osteoarthrosis (OA) receive multiple medical treatment options prior to undergoing total knee arthroplasty. It has been hypothesized that a treatment gap exists for patients with symptomatic knee osteoarthrosis who are unresponsive to conservative management yet are unsuitable or unwilling to undergo invasive surgical procedures. We review these medical and surgical techniques and discuss the role of orthobiologics for this subset of patients.

Keywords: Total knee arthroplasty, treatment gap, knee osteoarthrosis, knee osteoarthritis regenerative medicine

Introduction

Osteoarthrosis (OA) is one of the leading causes of disability and it is estimated that 14 million people in the United States have symptomatic knee OA [1]. It is the most common joint disorder in the United States and the incidence is likely to increase due to both the aging population and obesity epidemic. The risk factors for knee OA include age, genetic susceptibility, obesity, female sex, trauma, repetitive knee trauma, muscle weakness, joint laxity, kneeling, squatting, and meniscal injuries [2].

Although pain from knee OA can be severely debilitating, there still remains debate regarding the standard of care for these patients. Currently, first-line treatment for all patients with symptomatic knee OA involves conservative options including exercise, weight loss, knee bracing, and physical therapy [3]. Medications and supplements that have been recommended include oral and topical NSAIDs, acetaminophen, duloxetine, glucosamine, and chondroitin [4]. Additional treatments include: Transcutaneous Electrical Nerve Stimulation (TENS), and Pulsed Electromagnetic Field Therapy (PEMF), and Low Intensity Pulse Ultrasound (LIPUS) modalities. Curcumin may have benefits for pain and function and Cannabidiol (CBD) has shown benefits for OA in rat models [5,6].

Interventional procedures include intra-articular injections of corticosteroids, hyaluronic acid derivatives, platelet rich plasma, and cellular products [4]. Additional non-surgical treatments include essential oils, acupuncture, biomagnetism, and genicular nerve stimulation or ablation.

For patients in whom conservative treatments are not effective, surgical treatment is generally reccomended. Knee OA is the most common reason for a Total Knee Arthroplasty (TKA) [7].

TKA and OA Treatment Gap

TKA is the most commonly performed surgical procedure for knee OA7. It is estimated that 4.7 million Americans are currently living with a TKA with current estimates of 700,000 TKA performed each year [8]. By the year 2030, the number of procedures is expected to increase to 3.48 million annually [9,10]. This significant increase in TKAs has been attributed, in part, to the aging "baby boomer" generation and increased longevity8. The average cost of a primary TKA in the USA is $31,124 [11]. This cost includes the primary surgical intervention as well as claims submitted for pre-operative, and post-operative care. It should be noted that cost varies considerably by location from $20,575 in Charleston, SC to $50,062 in New York City, NY [12]. The total annual cost for the number of TKA performed each year in the US is currently about $10.2 billion [13].

The costs of complications following TKA have been studied. Clair et al. conducted a study evaluating the cost of complications after TKA. Surgical complications accounted for 44% of TKA readmissions and the average cost for these complications was $38,953 (range $4,790-$104,794). The average cost of medical complications after TKA was found to be $24,183 (range $3306-186,069) [12].

TKA revision surgery has been noted to cost an average of $75,028.07 [14]. Revisions may be required for various reasons with the most common being infection (20.4%) and mechanical loosening (20.3%) [14]. The lifetime risk of revision surgery has been found to trend inversely with age: risk decreases as one gets older. Notably, men in their 50s were found to have a 35% lifetime risk of requiring revision surgery for their TKA versus men and women in their 70s who incurred a lifetime risk of about 5% [15].

In order to optimize the treatment plan for patients with knee OA, it is important to understand the disease progression and when to apply treatment within it. Ferket et al. provided valuable insight into the value of delaying TKA and restricting its use to patients with more severe symptoms at baseline. The researchers assessed the quality of life benefit received from the TKA compared to the cost16. One of the outcome measures used was the SF-12 Physical Component Summary (PCS), a survey-based quality of life assessment. In this survey, those with lower scores on the SF-12 PCS have a lower quality of life due to their health than those with higher scores. This research found that in current practice, the lifetime likelihood of undergoing TKA was 39.9% (95% uncertainty interval 34.5 to 45.3) and surgery was performed on patients with SF-12 PCS scores as high as 55 [16].

The cost analysis in Ferket et al. provides evidence that it is economically favorable to only use TKA in more severely affected patients. They conclude that the optimal scenario would be to perform surgery for those with SF-12 PCS scores <35. The researchers predict that restricting TKA to those with a SF-12 PCS score < 35 would decrease the lifetime likelihood of TKA to 10.2% (95% uncertainty 8.1 to 12.4%) and save $6,974 (95% uncertainty $5789 to $8269) per patient, while only minimally lowering the effectiveness of treatment, demonstrated

by a slightly lower QALY -0.008 (-0.056 to 0.043). This was found to be the more effective scenario when compared to current practice in which surgery is performed on patients with SF-12 PCS scores as high as 55 [16].

Delaying the procedure, as Ferket et al. suggests, would cause more patients to live in what London et. al refers to as the "Osteoarthritis treatment gap" [17]. The treatment gap is the period between failed conservative treatment and future surgical intervention for patients with knee OA. Those patients in the treatment gap have been found to endure significant pain, impaired function, and a decreased quality of life [17]. Currently, 3.6 million Americans live in the treatment gap and this population is expected to grow to 5 million people by 2025 [17]. Identification of this population has led to the advancement of more treatment options for patients. This has introduced the role of Orthobiologic treatments such as Platelet Rich Plasma (PRP), Adipose Derived Mesenchymal Stem Cells (AD-MSC), Bone Marrow Derived Stem Cells (BM-MSC), Adipose Derived Stromal Vascular Fracture (SVF), Microfragmented Adipose Tissue (MFAT), and Bone Marrow Aspirate Concentrate (BMAC).

Orthobiologics

Regenerative treatments are gaining popularity as a potential treatment that may be a part of the solution to the treatment gap and improved care for patients with knee OA. These treatments are attractive as their autologous nature allows the patient to be both donor and recipient.

Currently, AD-MSCs and BM-MSCs do not meet regulatory compliance standards established by the US Food and Drug Administration as they are isolated and culture expanded. SVF's regulatory status is currently in question, but the US FDA's position is that it is not compliant. Studies evaluating AD-MSCs, BM-MSCs, and SVF were not included as part of this review due to their noncompliance with FDA regulations.

Platelet Rich Plasma (PRP) therapy

PRP is defined as an autologous blood product that contains elevated concentrations of platelets above that of whole blood [18]. There is a growing body of basic science and clinical evidence that supports the use of PRP for indications of mild to moderate knee OA. Zhu et al. noted that in culture, PRP has been shown to have anabolic effects on chondrocytes, resulting in cell proliferation, matrix production, and anti-inflammatory effects [19]. In an animal study, Kwon et al. induced knee OA via collagenase in a rabbit model to mimic human knee OA. Their study found that PRP imparted regenerative and chondroprotective benefits on cartilage in the rabbit model when compared to saline [20].

Meta-analyses of randomized controlled trials provide the best available evidence to evaluate the short-term effects on patients with knee OA undergoing PRP therapy. In 2017, Dai et al. performed a Level 1, meta-analysis of 10 RCTs (N=1069) comparing PRP intra-articular knee injections with saline and hyaluronic acid injections. When compared with saline, PRP was found to be more effective at pain relief and functional improvement according to WOMAC scores taken at 6 and 12 months post-injection. When comparing PRP and hyaluronic acid injections at 6 months post-injection, pain relief, and functional improvement were found to be similar. Extending the observation period to 12 months showed that PRP led to clinically and statistically significant, lasting improvements in pain relief and physical function when compared to hyaluronic acid according to the WOMAC [21].

In 2017, Shen et al. published a meta-analysis that studied 14 RCTs (N=1423) that concluded that PRP injections are probably more efficacious at treating pain and function associated with knee OA at 3, 6, and 12 months than saline placebo, HA, ozone, and corticosteroids.

Notably, PRP did not significantly increase the risk of post-injection adverse events [22].

In 2019, Han et al. published a meta-analysis that studied 15 RCTs (N=1,314) with evidence that indicates PRP reduced pain more effectively than hyaluronic acid injections at 6 and 12 months according to the WOMAC pain subscale. Functional improvement was found to favor PRP injections over hyaluronic acid injections at 3, 6, and 12 months post-procedure as well [23].

More recently, a 2020 study by Elik et al. studied 60 patients with knee osteoarthritis randomized into two groups: three 4 mL doses of intra-articular PRP and three 4 mL doses of intra-articular saline at one week intervals. Pain was measured with the Visual Analogue Scale, and functionality with the WOMAC. PRP was found to have significant positive effects on pain, physical function, and quality of life in patients over saline placebo [24].

While there are data that support the use of PRP in patients with mild to moderate knee OA, there are considerations to note when evaluating these studies. The autologous nature of PRP is intriguing because of its simplicity and safety profile, but there is a challenge of providing a reproducible product. Based on several factors both intrinsic and extrinsic to the patient, a product could vary. Furthermore, the optimal final-product contents of PRP have not yet been established in the literature and thus there is no standard for comparison in current research.

Classification systems for PRP products have been proposed, but not fully embraced. Mautner et al. proposes the PLRA (Platelet count, Leukocyte presence, Red blood cell presence and use of Activation) classification system. This classification system is based on contemporary literature, can be easily adopted for research, and reflects clinically important PRP characteristics. The authors identify the fundamental aspects of PRP that should be reported including cellular concentrations (platelets, WBCs [including neutrophils], and RBCs), presence or absence of exogenous activation, volume of PRP delivered, and frequency of PRP treatments if multiple treatments were delivered. Universal adoption of the PLRA classification system would provide an organized, effective method to scientifically approach the growing clinical exploration of PRP [25].

BMAC and MFAT

Two other orthobiologics we will consider are BMAC and MFAT. The two primary processes in current use for harvesting these tissues are bone marrow aspiration and lipoaspiration to obtain source tissues for development of BMAC and MFAT, respectively. Both are minimally invasive and well tolerated. Processing for MFAT and BMAC is consistent with the FDA regulations for use in daily medical practice. Without culture expansion, the process not compliant with FDA regulations, the final therapy is of a mixed cell product without a pure line of Mesenchymal Stem Cells (MSCs). Data indicates that MSCs make up only a small percentage of mononuclear cells in the BMAC, approximately 0.001% to 0.02% of the total nucleated cells [26]. Estimates of MSCs present in adipose or MFAT have not yet been made, but after processing lipoaspirate there is 5-50 times greater CFU-Fs compared with the same BMA tissue volume [27]. It has been postulated that the mechanism of the therapeutic effect of these treatments is multifactorial and occurs via angiogenic, anti-inflammatory properties, immune modulatory cytokines, and growth factors [28].

BMAC-the evidence

Studies evaluating the safety and efficacy of BMAC have included case reports, prospective clinical trials, retrospective studies, and randomized-controlled trials, and placebo-controlled comparative trials (Table 1). Kim et al. performed a prospective clinical trial evaluating the

effects of BMAC with an adipose tissue graft on 41 patients with knee OA. They found improvement with the VAS, IKDC, SF-36, KOOS, and Lysholm Knee Questionnaire at 12 months. Of note, the authors found that there was statistically significantly poor improvement across all scores in patients with K-L grade IV when compared to patients with K-L grades I-III which suggested that this intervention would be more effective in early to moderate knee OA [29]. However, Themistocleous et al. performed a retrospective cohort study on 121 specifically focusing on patients with K-L grade III or IV and found that patients who underwent BMAC treatments reported a mean NPS decrease from 8.33 to 4.49 ($p < 0.001$) and the mean OKS increased from 20.20 to 32.29 ($p < 0.001$) at a mean follow-up period of 11 months [30].

Table 1: Clinical Studies Evaluating BMAC for Knee OA.

Author	Type	Study Design	Number of Subjects	Number of Knees Injected	Guidance	Functional Outcome Measures	Results
Shapiro et al.	BMAC	Prospective, Single-Blind, Placebo-Controlled Trial (NS vs BMAC)	25	50	US	ICOAP, VAS	Significant improvement in ICOAP and VAS score with BMAC at 1 week, 3 months, and 6 months ($p < 0.12$ for all) Significant improvement in ICOAP and VAS scores with placebo (NS) ($p < 0.009$). No difference in ICOAP or VAS scores when comparing BMAC and placebo-treated knees ($p > 0.09$)
Centeno et al.	BMAC + PRP	Retrospective Cohort Study	681	840	US	LEFS, NPS	Significant improvement in LEFS and NSP score with BMAC at 12 months ($p = 0.03$)
Kim et al.	BMAC	Prospective Cohort Study	41	75	Not Reported	VAS, IKDC, SF-36, KOOS, LKQ	Improvement in VAS, IKDC, SF-36, KOOS, LKQ at 12 months. Improvement was significantly poorer in K-L IV group compared to K-L I-III groups.
Emadedin et al.	BMAC	Prospective, triple-blind, randomized, placebo-controlled trial	43	43	Not Reported	VAS, WOMAC, walking distance, painless walking distance, standing time, knee flexion	Significant improvement in WOMAC total score, WOMAC pain and physical function subscales, painless walking distance compared to placebo group at 6 months

Themistocleous et al.	BMAC	Retrospective Cohort Study	121	121	Not Reported	NPS, OKS	Significant improvement in NPS from 8.33 to 4.49 (p < 0.001) and the mean OKS increased from 20.20 to 32.29 (p < 0.001) at a mean follow-up period of 11 months
Garay-Mendoza. et al.	BMAC	Prospective Cohort Study	61	61	Not Reported	VAS, WOMAC	Significant improvement in knee pain and quality of life in BMAC treatment group compared to control group at 6 months follow up
Rodriguez-Fontan et al.	BMAC	Prospective Cohort Study	19	10	Fluoroscopy, US	WOMAC	Significant improvement in WOMAC score (p < 0.001) at 6 months (also included patients who underwent hip BMAC injections)
Anz et al.	BMAC vs PRP	Prospective, Randomized Clinical Trial	90	90	US	IKDC, WOMAC	All IKDC and WOMAC scores for PRP and BMAC significantly improved at 12 months after injections. There was no difference between PRP and BMAC at any time point.

Centeno et al. conducted a retrospective study evaluating the effects of BMAC for knee OA. Patients either received BMAC and PRP or BMAC, PRP< and an adipose fat graft. The mean Lower Extremity Functional Scale (LEFS) increased by 7.9 and 9.8 in the two groups, respectively, and the mean Numerical Pain Score (NPS) decreased from 4 to 2.6 and from 4.3 to 3 in the two groups, respectively. The improvements in both LEFS and NPS were statistically significant in both groups [31]. However, they reported better improvement in patients with K-L grades I or II when compared to patients with K-L grades III-IV similar to Kim et al. The authors demonstrated encouraging outcomes for BMAC and showed that an adipose graft does not provide any significant additional benefit.

There is a paucity of studies comparing BMAC to placebo and studies so far have demonstrated conflicting results. Emadedin et al. performed a triple-blind, randomized controlled trial in which 43 patients either received BMAC or saline injections. Patients who received BMAC experienced significantly greater improvements in WOMAC total score (p = 0.01), WOMAC pain (p = 0.001) and physical function (p = 0.04) subscales and painless walking distance (p= 0.02) compared with patients who received placebo after 6 months [32]. Shapiro et al. performed a prospective, single-blind, placebo-controlled trial comparing BMAC to placebo (saline). 25 patients with bilateral knee OA were administered BMAC in one knee and saline in the other. Knees treated with BMAC demonstrated a significant improvement in the ICOAP pain score from

baseline to 1 week, 3 months, and 6 months (p < 0.012). There was also a significant improvement according to ICOAP total pain scores in knees treated with placebo (saline) (p < 0.009). However, there was no significant difference in either ICOAP or VAS scores between knees treated with saline or BMAC (p > 0.09). The authors mentioned various explanations for the results including the potential systemic effects of MSCs and called for further studies with larger sample sizes [33]. Garay-Mendoza et al. treated patients with either oral acetaminophen or BMAC injection and reported statistically significant improvement in VAS and WOMAC scores in patients treated with BMAC at 6 months [34]. Other clinical studies evaluating the efficacy of treatment with BMAC are included in Table 1 [35,36].

Many of the studies evaluating the efficacy of BMAC support the use of BMAC for knee OA. Kim et al. reports better outcomes in patients with lower K-L grades whereas Themistocleous et al. report significant improvement with BMAC in patients to moderate to severe knee OA. It is difficult to compare all these aforementioned studies given the differences in study design, sources and doses of cells, and administration of adjuvant therapy. Further studies focusing on radiologic analyses of cartilage in addition to prospective, randomized, double-blinded, trials with larger sample sizes would better elucidate the efficacy of BMAC treatment for knee OA.

MFAT-the evidence

Multiple studies have demonstrated the safety and efficacy of MFAT with patients of all grades of knee OA suggesting that it may be an option for patients with grades K-L III and IV (Table 2). Barfod et al. performed a prospective cohort study on 20 patients and demonstrated statistically significant improvement in all KOOS subscales at the 1 year follow up [37]. Another prospective cohort study by Panchal et al. demonstrated significant improvement in pain and function according to NPRS, KSS, FXN, and LEAS scores at 12 months [38]. Heidari et al. performed a retrospective cohort study evaluating the effects of MFAT on 110 patients with symptomatic knee OA. Patients with all grades of knee OA who were treated with intra-articular injections of MFAT reported statistically significant improvements in pain, function, and quality of life. Pain according to the median VAS score significantly improved from 70 to 30 at 12 months (p< 0.001) and function according to OKS significantly improved from 26 to 33.5 (p < 0.001). Quality of life measured by the median EQ-5D significantly improved from 0.62 to 0.69 (p < 0.001) [39].

Table 2: Clinical Studies Evaluating MFAT for Knee OA.

Author	Type	Study Design	Number of Subjects	Number of Knees Injected	Guidance	Functional Outcome Measures	Results
Mautner et al.	MFAT vs BMAC	Retrospective Cohort Study	110	76	US	EQOL, VAS, KOOS	Both groups had significant improvement in all outcome measures (p< 0.01). There was no significant difference when comparing outcome measures between the two treatment groups.
Heidari et al.	MFAT	Retrospective Cohort Study	110	110	US	VAS, EQ-5D, OKS	Median VAS improved from 70 to 30 (p < 0.001), median OKS improved from 25 to 33.5 (p < 0.001), and median EQ-5D improved from 0.62 to 0.69 (p < 0.001)
Boric et al.	MFAT	Prospective Cohort Study	10	18	Not Reported	Delayed gadolium (Gd)-enhanced magnetic resonance imaging of cartilage (dGEMRIC), VAS	Contents of cartilage glycosaminoglycans significantly increased in specific areas of the treated knee joint. Resting VAS significantly decreased from 4.45 + 2.242 to 0.55+ 1.04 (p < 0.001) at 24 months and activity VAS decreased from 7.73 + 1.35 to 3.40 + 1.65 (p < 0.001).
Barford et al.	MFAT	Prospective Cohort Study	20	20	US	KOOS	Statistically significant improvement in all subscales of KOOS.
Panchal et al.	MFAT	Prospective Cohort Study	17	26	US	NPRS, KSS, FXN, LEAS	Mean KSS score significantly improved at 12 months. FXN score significantly improved from 65 to 76. LEAS score significantly improved from 36 to 47.

MFAT has also been studied to investigate their effect on proteoglycan synthesis in patients with knee OA. Boric et al. performed a prospective study on 17 patients with K-L grade III and IV and followed them up to 24 months. Only 10 of the 17 patients were included in the 24 months follow-up. They found that a single intra-articular injection of autologous MFAT significantly improved Glycosaminoglycan (GAG) content as over half of the measurements demonstrated relevant increase compared to an expected GAG decrease that knee OA traditionally leads to. Patients also demonstrated substantial pain relief as resting VAS significantly decreased from 4.45 + 2.242 to 0.55+ 1.04 (p < 0.001) at 24 months and activity VAS decreased from 7.73 + 1.35 to 3.40 + 1.65 (p < 0.001) [40].

Comparison studies between orthobiologics have been increasing as practitioners have the option of using PRP, BMAC, or MFAT as treatments for knee OA. Mautner et al. performed a retrospective study evaluating patients with symptomatic knee OA who received BMAC (41 patients) or MFAT (35 patients) injections. Both groups demonstrated significant improvement in EQOL, VAS, and KOOS (p < 0.001) at a mean follow up time of 1.8 + 0.88 years for BMAC and 1.09 + 0.49 years for MFAT. Notably, there were no significant differences when comparing the outcome measures between either treatment group. The authors concluded that both MFAT and BMAC significantly improve pain and function in patients with symptomatic knee OA without a significant difference in improvement when comparing the two treatments [28].

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Anz et al. performed a randomized prospective clinical trial comparing the efficacy of BMAC to PRP for the treatment of knee OA. 90 patients with K-L grade I to III were randomized to receive either BMAC or PRP. Patients for both PRP and BMAC treatment groups demonstrated significantly improved pain and function according to IKDC and WOMAC scores at 12 months. No significant difference in scores were seen between PRP and BMAC which suggests that either treatment may be used to improve pain and function for patients with mild to moderate knee OA [36].

Cost of orthobiologics

Due to the recent rise of orthobiologics, there have only been only a few studies reviewing the costs of these novel treatments. A study by Piuzzi et al. found that the current mean marketed price for a single same-day intra-articular injection of PRP is $714 (SD= $144; 95% Confidence Interval [CI] 691-737, n=153) [41]. Currently, PRP is not widely covered by health insurance companies for indications of knee OA. It is important to highlight that hyaluronic acid injections are covered by most insurance companies for indications of knee OA. As we have discussed, there have been promising results that favor PRP over HA and show that PRP is more beneficial for a longer period than HA injection.

Similar to PRP injections, MFAT and BMAC are not covered by most health insurance companies in the United States. Therefore, these types of therapies are paid for by the patient. In a separate study, Piuzzi et al. found that the current mean market price for unilateral, same day "stem-cell knee injection" was $5,156 (SD=$2,446; (95% CI [$4,550-5762] n=65 [42]. However, the actual "stem cell" product was unknown.

Conclusion

The total number and cost of TKA in the United States rises each year and will continue to place a significant burden on the healthcare industry if the management of knee osteoarthrosis remains unchanged. As discussed, the ideal patient population undergoing TKA are those who have more severe symptoms of knee OA. Patients with mild to moderate knee OA symptoms benefit from delaying TKA as the economic and quality of life costs have not been shown to outweigh the benefit of TKA at that stage in the disease progression.

Patients who fail conservative treatment of mild to moderate knee OA will likely seek out interventional treatments. Patients who then fail interventional treatment belong to a specific population known as the treatment gap in which they do not benefit from conservative treatment or interventional procedures and have yet to undergo a TKA. Regenerative therapies demonstrate a potential approach to treat this specific patient population.

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