Current Pain and Headache Reports (2019) 23:82
https://doi.org/10.1007/s11916-019-0822-9

HOT TOPICS IN PAIN AND HEADACHE (N. ROSEN, SECTION EDITOR)

Role of Alpha-2-Microglobulin in the Treatment of Osteoarthritic Knee Pain: a Brief Review of the Literature

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Abstract

Purpose of Review Chronic knee pain remains a debilitating condition that remains difficult to manage. The purpose of this review, therefore, is to summarize current understanding of alpha-2-microglobulin in the treatment of osteoarthritic knee pain. Furthermore, we investigate its role in the anti-inflammatory properties of platelet-rich plasma (PRP).

Recent Findings Alpha-2-microglobulin, a 720-kD protein complex, is an active protease inhibitor with tremendous anti-inflammatory properties in animal models. A growing body of evidence suggests that this complex is the most instrumental factor for cartilage preservation in PRP injections.

Summary As an active component of platelet-rich plasma's anti-inflammatory properties, alpha-2-microglobulin has been shown to be an active inhibitor of joint degeneration, cartilage preservation, and improvement in quality of life for patients with knee osteoarthritis compared with a multitude of other modalities.

Keywords Alpha-2-microglobulin · Proteinase · Platelet-rich plasma · Osteoarthritis

Introduction

Chronic knee pain is a debilitating condition that significantly impacts patient quality of life [1]. It is mediated by various non-traumatic rheumatic diseases, including fibromyalgia, gout, rheumatoid arthritis, and, most commonly, osteoarthritis (OA) [2]. OA affects over 30.8 million Americans each year and is characterized by the slow onset of articular cartilage loss within the tibiofemoral joint and concurrent degradation of its proteoglycan-rich extracellular matrix [3]. This degradation is strongly associated with painful synovitis and osteophyte formation [4, 5]. Because of the prevalence and profound impact of the disease, much research centers around factors related to the development and treatment of OA. Alpha-2-microglobulin (A2M) is an emerging treatment modality due to inhibitory properties that suppress proteinates that are harmful to cartilage and may prevent or limit OA. In the present investigation, we briefly review the diagnosis and

This article is part of the Topical Collection on *Hot Topics in Pain and Headache*

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Published online: 09 September 2019

management of OA before discussing emerging evidence surrounding A2M and its potential role in the management of OA.

Background

Osteoarthritis typically presents as joint pain and stiffness that increases over a period of years [6–8]. It is differentiated by pain that worsens with physical activity and improves with rest, though some patients experience joint stiffness in the early morning and following other periods of inactivity. Crepitus, joint locking, and joint instability may also be present. Physical examination may or may not find joint inflammation. Knee OA can additionally be diagnosed with radiography and more sensitive MRI. Radiography may demonstrate joint space narrowing and osteophyte formation, while MRI can detect OA in early stages through subtle morphological changes such as chondral softening and fissuring [9] and subchondral bone cysts, sclerosis, and increased density [7]. OA is often heterogenous in clinical presentation, and some patients may not experience symptoms despite radiographic confirmation of OA [10].

The etiology of OA is complex and potentially multifactorial. Of all risk factors, obesity and age are the most direct and concerning for knee OA. Age is the most predictive marker for knee OA. The incidence rate per person-year more than doubles between ages 50–59 and 60–69, possibly indicating a decrease of chondrogenesis over the latter stages of life [11]. Obesity is similarly associated with increasing frequency and severity of knee OA, due to increased joint loading [11]. Work that requires intense or repetitive physical stress to the joint is also associated with a several-fold increase over controls in the risk for developing knee OA [12]. Abnormal leg anatomy with varus and valgus knee alignment, significant leg length inequality, and abnormal tibial and femoral bone morphology similarly increase stress to the joint and increase risk for knee OA [13]. Such biomechanical abnormalities were less predictive than age, and most individuals with these abnormalities do not develop knee OA [13]. As the populations of many countries have and continue to become proportionally older [14] and more obese [15], the global prevalence of knee OA will become an increasing societal burden. OA is already one of the most common causes of disability and has been shown to preclude social and economic participation. In addition to social and work absenteeism, OA costs over $185 billion annually of health care resources [16].

OA pathophysiology involves not only striking alterations to articular cartilage but also other tissues proximal to the affected joint [17]. Articular cartilage ECM consists of water, type II collagen, and various proteoglycans, and it consists of chondrocytes which turnover collagen, an ability lost with age [17]. Surface fibrillations appear in early knee OA, developing into fissures that expose underlying bone and calcified cartilage. Disruption of chondrocyte pericellular matrix interferes with their collagen synthesis via altered signaling [17]. Loss of the collagen network renders cartilage susceptible to mechanical abrasion. In addition, loss of the collagen network and its protective proteoglycans throughout disease progression occurs with upregulation of proteinases and pro-inflammatory factors such as a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-7 and (ADAMTS)-12 [18, 19]; matrix metalloproteinases (MMP)-2, (MMP)-7, (MMP)-9, and (MMP)-13 [20]; and cytokines (IL-1β and TNFα) [20].

ADAMTS are a class of aggrecan- and cartilage oligomeric matrix protein (COMP)-cleaving proteinases, and MMPs are a group of enzymes including collagenases [18]. IL-1β and TNFα are pro-inflammatory and upregulate collagenase production in chondrocytes [20]. Increased chondrocyte expression of these catabolic and pro-inflammatory mediators further deregulates collagen synthesis and degrades existing ECM components [17]. Fragmentation of aggrecan (by MMP-2, MMP-7, MMP-9, and MMP-13) exposes its G3 domain, which allows formation of the fibronectin-aggrecan complex (FAC) [20]. This and aggrecan fragments alone exist in elevated concentrations in synovial fluid (SF) of OA patients as a product of cartilage degradation, so they can possibly serve as a biomarker to measure disease severity and treatment outcomes [21, 22].

Management of Osteoarthritis

A variety of non-surgical and surgical treatments have been established to manage knee OA. Pharmacotherapeutics such as non-steroidal anti-inflammatory drugs (NSAIDS) temporarily relieve joint pain and stiffness but are largely analgesic, without altering the course of the disease [23]. NSAIDS are associated with adverse effects such as GI bleed, particularly with long-term administration [5]. Intra-articular corticosteroid injection provides effective but transient analgesia [5]. Continuous injections carry risks of infection and joint tissue injury [24]. Glucosamine sulfate may be an effective treatment, but definitive evidence is lacking [25]. Lifestyle modifications such as weight loss for obese patients and moderate exercise are effective but difficult for many patients to sustain [26]. Physical therapy is moderately beneficial but similarly limited by poor patient adherence [27]. Surgical management is primarily comprised of arthroscopic debridement and partial or total knee replacement. However, evidence suggests that arthroscopy was non-superior to lavage and placebo in relieving pain and inflammation [5, 28]. High tibial osteotomy is effective against OA mediated by varus and valgus knee, but results are diminished in the obese and elderly, populations preferentially affected by knee OA [5]. Joint distraction may

be effective against OA in patients with varus knee [29], with valgus knee [5], and with unreported etiologies [30]. Improved prosthetics and surgical techniques make partial and total knee replacement more viable toward treating knee pain than previously, but they are still recommended as a last resort due to greater risk of complications [5].

Overall, among established knee OA treatments, no single modality has shown to effectively treat or reverse OA while maintaining acceptable cost, sustainability, and safety profile. Because a wide range of catabolic and pro-inflammatory proteins cause articular cartilage degradation, molecules that inhibit ADAMTS, MMPs, and cytokines are of great interest to slow articular cartilage degradation and prevent OA disease progression [17]. Alpha-2-microglobulin (A2M) is a glycoprotein found to be of interest for its chondrogenic, anti-inflammatory roles found in in vitro and animal studies. The role of A2M in OA has yet to be explored.

Alpha-2-Microglobulin Pharmacology

Human A2M is a 720 kDa, 1451 aa homotetrameric glycoprotein occurring primarily in serum at 1.5 mg/ml in healthy patients, and at approximately a tenth of that concentration in healthy SF [31]. It inhibits multiple proteinases of several classes via a sequestration mechanism [32]. Each pair of monomers contains a "bait region" that contains primary sequences able to be cleaved by many proteinases [33]. Cleavage of the bait region induces conformational changes of A2M that form a steric cage around the prey proteinase [19, 32]. Conformational change additionally activates thiol ester between cyc949 and glx952 and exposes 4 receptor binding domains, each of which is on the C-terminus of each monomer. Activated thiol esters rapidly form covalent bonds with nucleophilic sites on the prey proteinase, complexing it and A2M. Exposed receptor binding domains then permit binding of the A2M-proteinase complex to macrophage receptors and subsequent clearance of the complex [32].

Systematically, A2M in SF thus acts to reduce concentrations of various proteinases harmful to cartilage, potentially attenuating OA symptoms and encouraging chondrogenesis. A2M has been shown to inhibit ADAMTS-1, ADAMTS-4, ADAMTS-5, ADAMTS-7, and ADAMTS-12 in a dose-dependent manner [17, 18]. There is mild evidence that A2M inhibits MMP-13 in vivo [17]. A2M can additionally reduce cytokine-induced upregulation of collagenases in chondrocytes via trapping IL-1β and TNF-α [19], and one study demonstrated A2M decreased cartilage catabolism via inhibition of ADAMTS-5 and several MMPs in a bovine cartilage explant (BCE) model [19]. One rat ACLT OA model found A2M reduces MMP-13 concentration in SF, attenuating OA progression [31]. Perhaps the most promising study of A2M effects on OA to date, Zhang et al. designed A2M variants with modified bait regions to include native substrates for ADAMTS-4 and ADAMTS-5, MMPs, elastase, and cathepsin [34]. In this same study, a BCE model showed that A2M variants inhibited cartilage degradation by up to 200% comparted with wild-type A2M [34]. Furthermore, an anterior cruciate ligament transection rat OA model showed that wild-type A2M and its variants enhanced aggrecan and type II collagen synthesis, mitigated cartilage damage, and inhibited MMP-13 [34].

It is of note that A2M is present in higher concentrations in SF of OA patients, and so even native A2M is insufficient to treat OA [31]. Given A2Ms demonstrated chondrogenic and chondroprotective effects, intra-articular injections of supplemental A2M have been tested clinically to treat broader rheumatic conditions in several joints. A prominent technique for concentrating autologous A2M from patient blood is Autologous Platelet Integrated Concentration (APIC), developed by Cytonics (West Palm Beach, Florida) [19]. The office-based procedure requires 40 min, venous puncture, and special equipment.

Updates on the Use of Alpha-2-Microglobulin in Knee Osteoarthritis

A2M in Animal Studies

Numerous animal studies evaluate the chondroprotective effects of alpha-2-microglobulin (A2M). Wang et. al analyzed the effectiveness of alpha-2-microglobulin as an inhibitor of cartilage destruction in posttraumatic osteoarthritis [35]. In this study, rats underwent anterior cruciate ligament transection (ACLT) and A2M measurement using ELISA, western blotting, and mass spectrometry. Matrix metalloproteinase 13 (MMP 13) levels were significantly higher in the synovial fluid of rats with ACLT. However, rats receiving intra-articular A2M had reduced concentration of MMP-13, a favorable OA gene expression profile, and attenuated OA progression.

Cuellar et al. also studied OA progression following ACLT, instead using New Zealand White rabbits [36]. Treatment group rabbits received intra-articular injections of autologous platelet integrate concentrate on days 1, 4, and 14 post ACLT. Notably, the treatment group showed significantly less femoral and tibial degeneration than the control group. Alpha-2-microglobulin synovial fluid levels were 5- to 10-fold higher in the treatment group, further supporting a potential role for A2M in cartilage preservation.

Similarly, Tortorella et al. investigated the ability of A2M to attenuate proteinase ADAMTS-4 and ADAMTS-5 activity to prevent cartilage breakdown [37]. *Drosophila* cells were incubated with ADAMTS-4, ADAMTS-5, and A2M, resulting in a marked inhibition of ADAMTS-4 and

ADAMTS-5. This finding was attributed to the anti-proteinase properties of A2M and increased overall stability of the cartilage aggrecan.

A2M in Randomized Controlled Trials

Alpha-2-microglobulin has been isolated as a major contributor of platelet-rich plasma (PRP) injections, which have had promising results in human knee pathology. Several randomized controlled studies (RCT) document PRP's role in improving functionality and pain scores (Table 1). Cole et al. analyzed the clinical and biological efficacy of PRP injections vs hyaluronic acid (HA) [38]. This double-blinded RCT evaluated 111 patients with symptomatic unilateral knee pain receiving leukocyte poor PRP (LP-PRP) or HA intra-articular injections. Patients receiving PRP experienced statistically significant improvement in International Knee Documentation Committee (IKDC) scores and Visual Analog Scale (VAS) scores at 6 months follow-up. Similarly, Paterson et al. reported statistically significant improvements in VAS scores, Knee Injury and Osteoarthritis Outcome Score (KOOS), and Knee Quality of Life (KOoL), and knee range of motion among patients receiving intra-articular photo-activated PRP vs HA at 12 weeks follow-up [39]. In a double-blinded, randomized controlled trial evaluating intraoperative addition of LP-PRP vs placebo for degenerative knee lesions during arthroscopy, Duif et al. noted significantly lower pain scores and quality of life in the LP-PRP group at 6 months follow-up, but no major difference at 1 year [40].

Additional Studies

Several prospective studies report similarly promising results (Table 1). Spaková et al. performed a prospective study looking at HA vs PRP with knee and reported statistically significant improvement in Western Ontario and McMasters Osteoarthritis Index (WOMC) scores among all levels of OA severity at 3 and 6 months follow-up [41]. Kon et al. further compared the effectiveness of HA vs PRP for the prevention of cartilage degeneration [42]. One hundred fifty patients with severe OA received autologous PRP, low-weight HA, or 50 with high-weight HA. At 2 months follow-up, the high-weight HA group had greater relief, but at 6 months follow-up, the PRP group exhibited greater relief. PRP showed greater efficacy in younger patients and those with earlier stage OA. Finally, Charousst et al. evaluated the efficacy of subsequent injections of PRP for athletes with patellar tendinopathy (PT) [43]. This study reported improvement in Victorian Institute of Sport Assessment Patella (VISA-P), VAS, and Lysholm scores as well as improved structural integrity on MRI at 3 months follow-up with complete structural integrity in 57% of the study population at 2 years [43].

Li et al. performed a retrospective study comparing the safety and efficacy of intra-articular injections of PRP vs sodium hyaluronate in 30 patients (SH) [44]. Patients receiving PRP had significant improvement in IKDC scores, WOMAC scores, and Lequesne Index at 2 months and 6 months follow-up, but 12/15 patients in the PRP group noted minor adverse reactions (swelling, redness, tenderness of injection site).

Chen et al. published a case series describing the addition of HA to PRP injections for 3 patients with advanced knee OA (Table 1) [45]. The authors reported statistically significant improvement in VAS scores and joint height on x-ray. In a similar case series of 50 patients undergoing PRP injections, Gobbi et al. noted significant improvement in IKDC scores at 6 and 12 months [46]. Gibbs et al. also described marked improvement in the KOOS scores of four patients receiving a combination of exercise rehabilitation, stromal vascular fraction cells (Stromed), and PRP injections for knee OA [47]. Conversely, Bowman et al. published a case series of 3 patients who received PRP injections for knee pathology and subsequently developed worsening anterior knee pain and patellar tendon thickening at 6 months [48].

Future Directions

Clinical trials involving alpha-2-microglobulin in human subjects are currently ongoing. One such study will evaluate pro-inflammatory markers in synovial fluid after treatment with alpha-2-microglobulin [49]. A second study from Stanford University is currently in its recruitment stage and will involve the sampling of synovial fluid from patients undergoing total knee arthroplasty [50]. The synovial fluid of these subjects will be compared with patients with primary and secondary osteoarthritic joints for levels of protease inhibitor levels. PRP has been approved by the FDA's Center for Biologics Evaluation and Research (CBER) for use intra-operatively for orthopedic procedures. The use of PRP in the office setting is considered "off-label" at this time.

Conclusion

In summary, osteoarthritis is the most common cause of severe knee pain worldwide. It results in social and economic isolation of affected individuals and has tremendous healthcare-related costs. At present, no single treatment modality is simultaneously minimally invasive, cost efficient, feasible, and effective in the

Table 1 Characteristics of selected studies on PRP injections

First author, year	Study design and setting	Patient population	Treatment group	Injection protocol	Control group	Outcomes assessed	Pain assessment time-points	Analgesic outcomes	Adverse effects/study limitations
Charousset 2014	Prospective outpatient study	28 athletes with chronic PT refractory to non-operative management.	PRP injections ($n = 28$)	3 consecutive injections 1 week apart with ultrasound guidance.	None	VAS pain scores (0–10) VISA-P scores (0–100) Lysholm knee scores (0–100)	- Baseline - 3 months post injection - 6 months post injection - 2 years post injection	Improvement in all pain scoring systems at every time interval. MRI evidence of improved structural integrity at 3 months. Complete joint stability in 16 patients (57%).	Recalcitrant PT noted in 2 patients in study group.
Chen 2016	Case series, outpatient	3 patients with advanced knee OA.	PRP injections with HA ($n = 3$)	PRP injections with the addition of HA for 1 injection in all 3 patients.	None	VAS pain scores (0–10)	- Baseline - 1 year post injection - 2 years post injection	Improved noted in VAS scores in all 3 subjects. Standard weight-bearing x-rays at 2 years noting improvement in joint height and possible articular cartilage regeneration.	Small power of study. No standardization of standing knee x-rays to measure real articular cartilage changes.
Gobbi 2012	Case series, outpatient	50 patients with history of chronic knee OA. 25 patients had undergone previous operative intervention.	PRP injections ($n = 50$)	PRP injections at 0, 6, and 12 months.	None	IKDC scores (0–100)	- Baseline - 6 months - 12 months	Noted improvement in IKDC scores ($P < .001$) in both the operative and non-operative groups.	- No control group was a major limitation of this study.
Gibbs 2015	Case series, outpatient	4 patients with severe knee OA.	PRP injections, Stromed injections, and exercise rehabilitation ($n = 4$).	Combination of PRP injections Stromed injections at 0, 1, 2, 3, and 4 months.	None	KOOS scores (0–100).	- Baseline - 1, 2, 3, 4 months	Noted improvement in all patient's KOOS scores. All patients had significant improvement in "Get Up and Go Test" as well as "Stair Climbing Test".	- Changes may be due to placebo effect. - Hard to determine which component (PRP, exercise, Stromed) was the greatest contributor. - Short length of study. - Small study size
Bowman 2014	Case series, outpatient	3 patients who developed worsening PT after PRP injections.	PRP injections ($n = 3$)	PRP injections at 0. 2, and 6 months	None	None	Patellar tendon thickening, worsening pain, osteolysis of distal pole of patella in 1 patient needing	Patellar tendon thickening, worsening pain, osteolysis of distal pole of patella in 1 patient needing surgical intervention.	- Small sample size.

Table 1 (continued)

First author, year	Study design and setting	Patient population	Treatment group	Injection protocol	Control group	Outcomes assessed	Pain assessment time-points	Analgesic outcomes	Adverse effects/study limitations
							surgical interven-tion. −6 months post last PRP injection.		
Spaková 2012	Prospective, double--blinded randomized controlled trial	120 patients with Grades 1, 2, or 3 OA based on Kellgren and Lawrence scales.	PRP injections (n = 60)	PRP injections at 0, 3, and 6 months	HA injections (n = 60).	Western Ontario and McMast-ers OA index scores.	- Baseline - 3 months - 6months	Significant improvement in scoring in PRP group over HA group at 3 and 6 months.	- None
Kon 2011	Prospective, double--blinded randomized controlled trial	150 patients with severe knee OA.	PRP injections (n = 50)	PRP injections at 0, 2, and 6 months.	Low-molecular weight HA (n = 50) High-molecular weight HA (n = 50)	VAS scores (0–10)	- Baseline - 2 months - 6 months	- At 2 months follow-up, the low-molecular weight HA and PRP had similar results, with better efficacy noted in the high-weight HA group (P < .005) - At 6 months follow-up, better results were noted in the PRP group (P < .005) than either the high or low weight HA groups.	- None
Cole 2017	Double-blinded, randomized controlled trial, outpatient	111 patients with symptomatic unilateral knee pain due to mild to moderate knee OA.	PRP injections (n = 50)	Leukocyte-poor PRP injections at 0 and 6 months.	HA injections (n = 61)	- IKDC scores (0–100) - VAS scores (0–10)	- Baseline - 6 months	Significant improvement in IKDC scores at 6 months in PRP group. Notable improvement in VAS scores in PRP group.	Synovial fluid aspiration noted significantly higher levels of IL-6 in the PRP group at 6 months than the HA group.
Patterson 2016	Double-blinded, randomized controlled trial, Outpatient	37 patients with previously diagnosed knee OA.	Photo-activated PRP injections (n = 20)	Photo-activated PRP injections at 0, 3, and 12 weeks	HA injections (n = 17).	- VAS pain scores (0–10) - KOOS scores (0–100) - KQoL scores (0–100)	- Baseline - 12weeks	PA-PRP group demonstrated significant improvements in VAS (P < .01), KOOS pain (P < .05), and Knee Quality of Life (KQoL) (P < .05). Significant improvement in bending and hopping ability of the PRP group.	Minor pain and swelling noted from 2 patients in the PA-PRP group.
Duif 2015	Double-blinded randomized controlled trial, Inpatient	58 patients undergoing arthroscopic knee surgery for meniscal or cartilage degeneration	Leukocyte-poor PRP added intra--operatively (n = 24).	1 intra-operative injection.	Patients receiving no PRP injection intra--operatively (n = 34).	VAS pain scores (0–10).	-Baseline - 6 months - 12 months	Pain significantly lower in LP-PRP group (VAS 0.9 vs 2.3) at 6 months, but not at 12 months (VAS 1.0 vs 1.6 P = 0.063).	Assessment of life quality concerning physical component was significantly higher in LP-PRP at 6 weeks and 6 months, but equal at 1 year.
Li 2011	Double-blinded randomized	30 patients with knee articular	PRP injections at 0, 2, 4, and		SH injections.		- Baseline - 2 months	Significant differences existed in IKDC scores WOMAC scores, and Lequesne	- Minor self-limiting skin irritation noted in 12

Table 1 (continued)

First author, year	Study design and setting	Patient population	Treatment group	Injection protocol	Control group	Outcomes assessed	Pain assessment time-points	Analgesic outcomes	Adverse effects/study limitations
	controlled trial, Outpatient	cartilage degeneration.	6 months ($n = 15$).	Intra-articular PRP injections.		- IKDC scores (0–100) - WOMAC scores (0–100) - Lequesne Index	- 6 months	Index between the two groups at 2 months follow up.	patients of the treatment group.
Cole 2017	Double-blinded, randomized controlled trial, Outpatient	111 patients with symptomatic unilateral knee pain due to mild to moderate knee OA.	PRP injections ($n = 50$)	Leukocyte-poor PRP injections at 0 and 6 months.	HA injections ($n = 61$)	- IKDC scores (0–100) - VAS scores (0–10)	- Baseline - 6 months	Significant improvement in IKDC scores at 6 months in the PRP group. Notable improvement in VAS scores in the PRP group.	Synovial fluid aspiration noted significantly higher levels of IL-6 in the PRP group at 6 months than the HA group.
Patterson 2016	Double-blinded, randomized controlled trial, Outpatient	37 patients with previously diagnosed knee OA.	Photo-activated PRP injections. ($n = 20$)	Photo-activated PRP injections at 0, 3, and 12 weeks	HA injections ($n = 17$).	- VAS pain scores (0–10) - KOOS scores (0–100) - KQoL scores (0–100)	- Baseline - 12 weeks	PA-PRP group demonstrated significant improvements in VAS ($P < .01$), KOOS pain ($P < .05$), and Knee Quality of Life (KQoL) ($P < .05$). Significant improvement in bending and hopping ability of the PRP group.	Minor pain and swelling noted from 2 patients in the PA-PRP group.
Duif 2015	Double-blinded randomized controlled trial, Inpatient	58 patients undergoing arthoscopic knee surgery for meniscal or cartilage degeneration	Leukocyte-poor PRP added intra--operatively ($n = 24$).	1 intra-operative injection.	Patients receiving no PRP injection intra--operatively ($n = 34$).	VAS pain scores (0–10).	- Baseline - 6 months - 12 months	Pain significantly lower in the LP-PRP group (VAS 0.9 vs 2.3) at 6 months, but not at 12 months (VAS 1.0 vs 1.6 $P = 0.063$).	Assessment of life quality concerning physical component was significantly higher in LP-PRP at 6 weeks and 6 months, but equal at 1 year.
Li 2011	Double-blinded randomized controlled trial, Outpatient	30 patients with knee articular cartilage degeneration.	PRP injections at 0, 2, 4, and 6 months ($n = 15$)	Intra-articular PRP injections.	SH injections.	- IKDC scores (0–100) - WOMAC scores (0–100) - Lequesne Index	- Baseline - 2 months - 6 months	Significant differences existed in IKDC scores, WOMAC scores, and Lequesne Index between the two groups at 2 months follow-up.	- Minor self-limiting skin irritation noted in 12 patients of treatment group.

PRP, platelet-rich plasma; *PT*, patellar tendinopathy; *VAS*, visual analog score; *VISA-P*, Victorian Institute of Scoring Assessment-Patellar; *HA*, hyaluronic acid; *IKDC*, International Knee Documentation Committee; *KOOS*, Knee Osteoarthritis Outcome Score; *OA*, osteoarthritis; *WOMAC*, Western Ontario and McMasters

treatment of OA and related pain. Alpha-2-microglobulin has had promising early results in animal and human studies. However, molecular and macroscopic mechanisms of OA etiology are poorly understood. Ongoing investigation will help determine the effect of novel knee OA therapeutics in countering the development and progression of OA. Future human clinical studies may help determine the role of A2M in the management of OA.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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