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Short-term comparison of intraarticular administration of IL-1 receptor antagonist and platelet-rich plasma for osteoarthritis treatment

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Abstract

Osteoarthritis (OA) is a prevalent joint condition that affects areas such as the knee, hip, hand, and spine. In treating mild to moderate cases of OA, treatment options such as intraarticular corticosteroids, viscosupplementation, glucosamine and chondroitin sulfate, PRP, and IL-1Ra are commonly used. This study aimed to compare the effects of IL-1 receptor antagonist (IL-1Ra) and platelet-rich plasma (PRP) on patients with Kellgren-Lawrence (KG) stage 2-3 knee osteoarthritis in terms of Visual Analog Scale (VAS) and Knee injury and osteoarthritis outcome score (KOOS). Ninety patients with KG stage 2-3 knee primary osteoarthritis were divided into two groups, with one group receiving three intraarticular IL-1Ra injections and the other group receiving three PRP injections. VAS and KOOS scores were recorded at the beginning and after six months to evaluate clinical improvement. Both the IL-1Ra and PRP groups showed statistically significant improvement in all scores, including the VAS and KOOS. After six months, the KOOS score in the IL-1Ra group was significantly higher than the PRP group, while the first-year VAS score after treatment in the IL-1Ra group was significantly lower compared to the PRP group. The mean KOOS scores increased from 44.1 to 87.8 and 46.04 to 84.43 at the end of six months in both groups, while the mean VAS scores decreased from 7.27 to 1.02 and 7.29 to 1.71 in the IL-1Ra and PRP groups, respectively. Administering intra-articular IL-1Ra once a week for three weeks can effectively improve function and reduce pain in patients with Kellgren-Lawrence stage 2-3 osteoarthritis. However, more research is necessary to validate the use of IL-1 receptor antagonists in OA treatment.

Keywords: Osteoarthritis, knee, interleukin-1, receptor, antagonist, cytokines, platelet rich plasma, cartilage, hyaluronic acid

Introduction

Osteoarthritis (OA) is a joint disorder characterized by reduced mobility, joint pain, and stiffness that is more prevalent with age and can significantly impact one's quality of life [1] Multiple treatment options are available to manage OA symptoms and associated cartilage damage, including non-steroidal anti-inflammatory drugs (NSAIDs), analgesics, corticosteroids, viscosupplementation, glucosamine, and chondroitin sulfate [2]. One promising treatment option is Platelet Rich Plasma (PRP), which utilizes growth factors found in platelets to naturally stimulate the healing process. PRP is known to possess anti-inflammatory and antibacterial properties, and has been shown to relieve pain associated with OA [3].

The primary cytokines associated with inflammation are interleukin-1 (IL-1) and IL-6, which have been linked to an increased risk of OA [4]. IL-1 is the main cytokine responsible

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for the symptoms of inflammation in OA [5,6]. Controlling the disease process involves inhibiting the effects of IL-1 through its natural inhibitor [7]. Targeted inhibition of IL-1 production and activity is a potential treatment option for osteoarthritis, which can be achieved through the use of a human recombinant IL-1Ra. [8]. The effectiveness of IL-1Ra has been observed in patients with rheumatoid arthritis, a systemic autoimmune disorder that impacts the joints and can negatively affect function, quality of life, and increase morbidity and mortality [1,2].To address this, a systemic form of recombinant IL-1Ra has been proven effective in reducing joint inflammation and alleviating the destructive effects of rheumatoid arthritis [9]. A systematic review of 592 patients with mild to moderate knee osteoarthritis found that intraarticular IL-1Ra was safe, tolerable, and may improve pain and functional outcomes [10].

In this study, we retrospectively assessed the effectiveness of intraarticular IL-1Ra treatment in Grade 2-3 osteoarthritis patients and compared these results with those of PRP intraarticular administration, which is a common clinical practice.

Material and Methods

The study was approved by the ethics committee of Medipol University (reference number 1080098-604.01.01-E.52357) on November 30, 2018. The data for this retrospective study was collected from the medical records of 122 osteoarthritis patients who had received intraarticular injections between March 2016 and January 2018, and were initially classified as stage 2-3 according to the Kellgren-Lawrance (KL) classification [11]. The patients were divided into two groups, with a total of 77 patients being evaluated in the study. The PRP group consisted of 40 women and 5 men, with an average age of 55.29 and an average Body-Mass Index (BMI) of 32.42, while the IL-1RA group consisted of 37 women and 8 men, with an average age of 56.13 and an average BMI of 32.39. Thirty-two patients were excluded from the study due to a history of knee surgery, prior intra-articular knee injections within the last year, or use of analgesics or anti-inflammatory drugs in the three months leading up to the injections.

The PRP preparation and administration were performed by a single investigator (Y.G) with a consistent and uniform approach for each patient. Peripheral blood was collected from the antecubital region in tubes containing 3.2% sodium citrate, following the guidelines of Anitua [12,13]. The tubes were centrifuged at 1800 rpm for eight minutes at room temperature, and 1 ml of the resulting 3.5 ml of PRP was sent for laboratory analysis, including bacteriological examination and platelet counting. The activated 2.5 ml PRP, which contained 5.5% calcium chloride (CaCl2), was then administered through the anterolateral portal under sterile conditions. After the intraarticular injection, patients were kept in a supine position for 15 minutes for observation. The same approach was also used for the administration of IL-1RA to the patients in the other group.

The same investigator (Y.G) performed the preparation of IL-1RA. A total of 10 mL of blood was drawn from the arm vein using a cannula and transferred to the Sanakin® kit (Scientific Biotech Germany) with a new cannula. The kit was gently rotated 3-4 times and incubated at 37°C for up to 3 hours. After the incubation process, the kit was centrifuged for 5 minutes at 4,000 RPM. The serum was then separated from the coagulated blood using a 5 mL Luer-Lock® syringe, resulting in an average of 3-4 mL of serum with a concentration of around 3000 pg/mL [14].

The conditioned serum that was prepared from the patient's own blood was then immediately administered through the anterolateral portal under sterile conditions. Following the injection, the patients were monitored while lying in a supine position for 15 minutes to observe for any adverse effects.Both groups received intraarticular injections through the anterolateral portal, which has been shown to provide high intraarticular distribution and low soft tissue infiltration, according to Esenyel et al. [15].

The clinical status of the patients was assessed using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and the Visual Analog Scale (VAS) during the first year of treatment. The KOOS has been validated to have good internal consistency, test-retest reliability, and construct validity for individuals with knee injury and/or osteoarthritis, including older adults [16].

Statistical Analysis

For the purpose of descriptive statistics, the researchers used measures such as mean, standard deviation, median, minimum and maximum values, frequency, and percentage. They also assessed the distribution of variables through the Kolmogorov-Smirnov test. To compare quantitative data, they used the Independent Samples t-test and Mann-Whitney U test. The Wilcoxon test was used for repeated measurement analysis, while the Chi-Square test was used for the comparison of qualitative data. All statistical analyses were performed using SPSS 27.0 software.

Results

This study involved a total of 90 patients, with 77 (85.6%) being male and 13 (14.4%) being female. Of these patients, 2 (2.2%) were classified as Grade I, 32 (35.5%) as Grade II, and 56 (62.2%) as Grade III according to the KL classification. The average age of the patients was 55.71, with an average pre-treatment KOOS score of 45.07 and an average VAS score of 7.28 (Table 1) ($p < 0.05$).

In the IL-1Ra and PRP groups, the average age of the patients was 56.13 and 55.29, respectively. In the IL-1Ra group, 37 (82.2%) were male and 8 (17.8%) were female, while in the PRP group, 40 (88.9%) were male and 5 (11.1%) were female. After six months of treatment, the mean KOOS scores in the IL-1Ra group increased from 44.1 to 87.8 and from 46.04 to 84.43 in the PRP group. The mean VAS scores also decreased, from 7.27 to 1.02 in the IL-1RA group and from 7.29 to 1.71 in the PRP group (Table 2) ($p < 0.05$).

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Table 1. KOOS and VAS scores before and after injection

		Min-Max	Median	Mean±sd/n-%
Age		34.00-70.00	55.00	55.71±6.57
Gender	Female		13	14.4%
	Male		77	85.6%
BMI		23.90-43.00	33.05	32.40±3.67
Grade	I		2	2.2%
	II		32	35.6%
	III		56	62.2%
KOOS		20.70-81.50	44.15	45.07±12.92
VAS		3.00-10.00	8.00	7.28±1.44

BMI: Body-Mass Index. KOOS: Knee Injury and Osteoarthritis Outcome Score VAS:Visual Analogue Scale

There were no statistically significant differences between Group 1 and Group 2 in terms of patient age, gender, Body Mass Index (BMI), and degree of disease, as indicated by Table 2 ($p>0.05$).

The study found that there was no significant difference in the pre-treatment KOOS scores between the IL-1RA and PRP groups ($p>0.05$). However, after 6 months of treatment, the KOOS scores in the PRP group were significantly higher than those in the IL-1RA group ($p<0.05$). Both groups showed a significant increase in KOOS scores after 6 months of treatment compared to their pre-treatment values ($p<0.05$). Moreover, the increase in KOOS scores in the PRP group was significantly greater than that in the IL-1RA group at the 6-month mark ($p<0.05$). These findings are presented in Table 2 and Figure 1.

The pre-treatment VAS values did not show significant differences between Group 1 and Group 2 ($p>0.05$). However, the VAS values at the 6-month mark in Group 2 were significantly lower than those in Group 1 ($p<0.05$). Both groups showed significant decreases in VAS values after 6 months of treatment compared to their pre-treatment values ($p<0.05$). Specifically, the decrease in VAS values at the 6-month mark in Group 2 was significantly greater than in Group 1 ($p<0.05$), as shown by Table 2 and Figure.

Table 2. KOOS and VAS scores differentitation based on injection type

		PRP		IL-1Ra		p
		Mean±sd/n-%	Median	Mean±sd/n-%	Median	
Age		55.29±7.86	55.00	56.13±5.01	55.00	0.545[t]
Gender	Female	5 11.1%		8 17.8%		0.368[x2]
	Male	40 88.9%		37 82.2%		
BMI		32.42±4.08	33.10	32.39±3.26	32.60	0.881[m]
Grade	I	1 2.2%		1 2.2%		
	II	17 37.8%		15 33.3%		0.664[x2]
	III	27 60.0%		29 64.4%		
KOOS	Before Treatment	46.04±16.23	44.60	44.10±8.50	44.00	0.806[m]
	6.Month	84.43±6.15	85.60	87.80±5.75	88.90	0.006[m]
	Intra Group Difference	38.39±14.28	39.80	43.67±9.30	45.10	0.049[m]
	Intra Group p	0.000[w]		0.000[w]		
VAS	Before Treatment	7.29±1.55	8.00	7.27±1.34	7.00	0.711[m]
	6.Month	1.71±1.36	2.00	1.02±0.97	1.00	0.010[m]
	Intra Group Difference	5.58±1.56	-5.00	-6.20 ± 1.67	-7.00	0.046[m]
	Intra Group p	0.000[w]		0.000[w]		

[t]t test /m Mann-whitney u test / X^2 Chi-square test / [w] Wilcoxon test
BMI: Body-Mass Index KOOS: Knee Injury and Osteoarthritis Outcome Score VAS:Visual Analogue Scale

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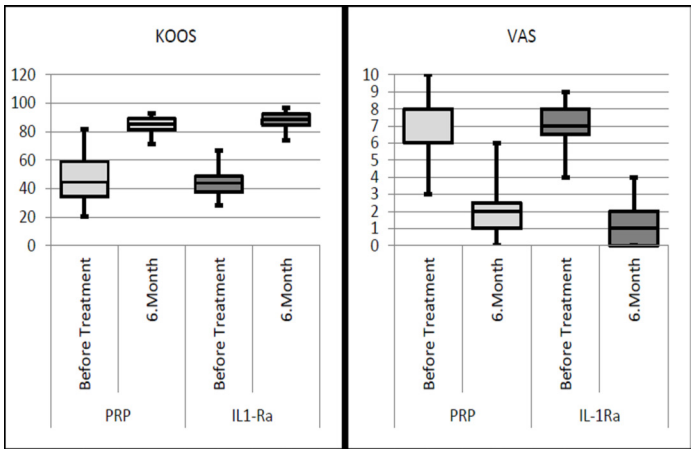

Figure 1. KOOS and VAS score improvement based on injection type

Discussion

The management of osteoarthritis is evolving, with an increasing focus on utilizing growth factor agents derived from an individual's own cells. PRP is currently the most commonly used of these agents. IL-1Ra represents another biological option for the treatment of osteoarthritis. In vitro and in vivo studies have demonstrated that IL-1Ra plays a significant role in the initiation and progression of cartilage destruction in the joints, due to its pro-inflammatory and catabolic properties as a cytokine [17].

PRP contains several mediators that are essential for tissue healing and bone regeneration, including platelet-derived growth factor, transforming growth factor, vascular endothelial growth factor, insulin-like growth factor, and various proteins such as fibrin, fibronectin, vitronectin, and thrombospondin [18]. PRP exerts beneficial effects on joint health, including regulation of blood vessel formation, protection and promotion of cartilage growth, stimulation of cell differentiation, modulation of synovial cells, and regulation of inflammation through its growth factors and proteins. It should be noted that PRP is more complex than previously thought and does not have a single mechanism of action in addressing joint issues [19]. Previous research has demonstrated the efficacy of PRP when administered twice with a one-month interval [20], three times every 21 days [21], four times on a weekly basis [22], and even with a single dose [23].

In addition, PRP therapy poses no risk of immune reaction or disease transmission since it utilizes the patient's own blood. Moreover, there have been no reported cases of hyperplasia, carcinogenesis, or tumor growth associated with PRP therapy. While mild to moderate pain or swelling may occur in some patients, severe local inflammation, warmth, and joint effusion are rare [24]. In the present study, there were no serious complications observed, except for a few patients (8 in the PRP group and 6 in the IL-1Ra group) who experienced local pain and swelling, which was managed with the use of paracetamol and cold compresses over a few days.

Elevated levels of IL-1Ra protein in plasma have been found to correlate with the severity of osteoarthritis, indicating it as a risk factor for symptomatic knee osteoarthritis over a 24-month follow-up period. Moreover, the severity of symptomatic knee osteoarthritis is associated with higher Western Ontario and McMaster Universities Arthritis Index (WOMAC) and VAS scores [25,26]. Recombinant human IL-1 receptor antagonist proteins work as competitive inhibitors of IL-1, preventing its effect without causing an agonist response [5].

The fact that a single injection of IL-1 can lead to both synovitis and loss of cartilage proteoglycans supports the hypothesis that this cytokine plays a crucial role in inflammatory joint diseases and that blocking its effects could have therapeutic benefits [27].

The role of IL-1 in osteoarthritis has prompted efforts to suppress its activity locally in the joint, despite some controversy in the literature. However, we have included it in our intra-articular treatment protocols. Several in vitro and animal studies have shown that recombinant human IL-1Ra has a positive impact on the structural modifications and symptoms of osteoarthritis. [28] Zhang et al. conducted an in-vivo study in a rabbit model of osteoarthritis to investigate the potential gene therapy application of co-expressing IL-1Ra and TGF-β1 to alter disease progression. The expression of IL-1Ra and TGF-β1 in tissues was correlated with a reversal of the disease in the experimental group, suggesting that co-expression of IL-1Ra and TGF-β1 can inhibit degeneration and improve the repair of articular cartilage in osteoarthritis [29].

Wang et al. conducted a study on rat and human osteoarthritis chondrocytes to investigate the effect of combining IL-1Ra with an autophagy inducer (TAT-Beclin1) on extracellular matrix degradation. Their findings demonstrated a reduction in matrix degradation with the combination treatment [30]. In another study involving 376 patients divided into three groups, the clinical effect of IL-Ra antagonist protein on knee osteoarthritis was evaluated. The results showed a 20% difference in WOMAC scores between IL-1Ra and hyaluronic acid (HA), as well as between HA and placebo. When intraarticular IL-1Ra protein with HA or placebo was compared using primary outcome variables, the effects of Interleukin-1 receptor antagonist protein were significantly superior to both HA and placebo. These findings suggest that IL-1Ra injection can provide clinical symptom improvement and positive results in patients with KOA [31].

Rutgers et al. examined the impact of IL-1Ra on cartilage proteoglycan metabolism and cytokine production in vitro. The goal was to explore its potential to protect cartilage and modify the disease. However, there was no significant difference observed between the use of IL-1RA and saline [32]. In a multicenter, randomized, double-blind, placebo-controlled trial, the effects of a single dose of 50 mg and 150 mg of IL-1Ra were studied in patients with osteoarthritis. Both doses were found to be well-tolerated after 12 weeks, but did not show any improvement in OA symptoms [33]. In a cohort study conducted by Auw Yang et al., the effect of IL-1Ra injection on reducing symptoms was found

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to be controversial. The study revealed significant improvement in the KOOS Score, symptoms, and sports parameters. However, the targeted recovery level could not be achieved even after six injections during the 12-month follow-up period, so the use of IL-1Ra injection is not recommended [34].

Our study demonstrated significant improvement in the VAS and KOOS for all patients who received weekly intra-articular injections of IL-1Ra. Based on these findings, we suggest that administering 3-5 ml of IL-1Ra three times a week is an effective short-term treatment for osteoarthritis. At the 6-month follow-up, all patient groups demonstrated statistically significant increases in knee function scores and decreases in pain scores compared to their baseline values. Moreover, patients in the IL-1Ra group showed greater improvement in both functional and pain scores when compared to other groups.

IL-1Ra has been found to be superior to PRP in the treatment of various conditions due to its direct suppression of IL-1, a key cytokine involved in inflammation [3]. Vangsness et al. conducted studies on the relationship between PRP and IL-1Ra content, and found that PRP contains high levels of IL-1Ra that can be further increased through plasma concentration [35]. This elevated level of IL-1Ra may explain the mechanisms behind the effectiveness of PRP in various applications. Therefore, the presence of IL-1Ra may play a crucial role in the effectiveness of PRP. The findings of elevated levels of IL-1Ra in PRP may help explain why IL-1Ra demonstrated greater effectiveness in our patients.

Limitations

This study has several limitations that should be taken into consideration. Firstly, there was no comparison made with other injectable treatments commonly used for osteoarthritis, such as steroids or stem cells. Secondly, the follow-up period was relatively short and the study participants were heterogeneous in terms of age, disease severity, and comorbidities. Finally, the sample size was relatively small, which may limit the generalizability of the results.

Conclusion

Although IL-1Ra demonstrated greater efficacy, both IL-1Ra and PRP were effective in improving function and alleviating pain in patients with grade 2-3 osteoarthritis when administered once a week for three weeks via intra-articular injection. Nonetheless, further research is required to confirm the utility of IL-1 receptor antagonists in the management of OA.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The study was approved by the ethics committee of Medipol University with the reference number 1080098-604.01.01-E.52357 on 30/11/2018.

References

1. Felson D, Naımark T, Anderson A, et al. The prevalence of knee osteoarthritis in the elderly. The framingham osteoarthritis study. Arthritis Rheum. 1987;30:914-8.
2. Fajardo M, Dı Cesare PE. Disease-modifying therapies for osteoarthritis: current status. Drugs Aging. 2005;22:141-61.
3. Sanchez M, Anıtua E, Orıve G, et al. Platelet-rich therapies in the treatment of orthopaedic sport injuries. Sports Med. 2009;39:345-54.
4. Goldring MB, Berenhaum F. The regulation of chondrocyte function by proinflammatory mediators: prostaglandins and nitric oxide. Clin Orthop Relat Res. 2004;427:37-46.
5. Pelletier JP, Martel-Pelletier J, Raynauld JP. Most recent developments in strategies to reduce the progression of structural changes in osteoarthritis: today and tomorrow. Arthritis Rsx Ther. 2006;8:206-19.
6. Valdes AM, Spector TD. The clinical relevance of genetic susceptibility to osteoarthritis. Best Pract Res Clin Rheumatol. 2010;24:3-14.
7. Arend WP, Malyak M, Guthridge CJ, Gabay C. Interleukin-1 receptor antagonist: role in biology. Annu Rev Immunol. 1998;16:27-55.
8. Seckinger P, Klein-Nulend J, Alander C, et al. Natural and recombinant human Il-1 receptor antagonists block the effects of Il-1 on bone resorption and prostaglandin production. J Immunol. 1990;145:4181-4.
9. Jiang Y, Genant HK, Watt I, et al. A multicenter, double-blind dose-ranging randomized placebo-controlled study of recombinant human Il-1 recetor antagonist in patients with rheumatoid arthritis: radiologic progression and correlation of genant and larsen Scores. Arthritis Rheum. 2000;43:1001-9.
10. Ajrawat P, Dwyer T, Chahal J. Autologous interleukin 1 receptor antagonist blood-derived products for knee osteoarthritis: a systematic review. Arthroscopy. 2019;35;2211-21.
11. Kellgren JH, Lawrance JS. Radiological assessment of osteoarhrosis. Ann Rheum Dis. 1957;16:494-502.
12. Anıtua E. Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. Int J Oral Maxillofac Implants. 1999;14:529-535.
13. Anıtua E, Andıa I, Ardanza B, et al. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost. 2004;91:4-15.
14. Meijer H, Reinecke J, Becker C, et al. The production of anti-inflammatory cytokines in whole blood by physicochemical induction. Inflammat Res. 2003;52:404-7.
15. Esenyel C, Demirhan M, Esenyel M, et al. Comparison of four different intra-articular injection sites in the knee: a cadaver study. Knee Surgery, Sports Traumatology, Arthroscopy. 2006;15:573-7.
16. Collins NJ, Prinsen CAC, Christensen R, et al. Knee injury and osteoarthritis outcome score (KOOS): systematic review and meta-analysis of measurement properties. Osteoarthritis Cartilage. 2016;24:1317-29.
17. Goldring MB. The role of cytokines as inflammatory mediators in osteoarthritis: lessons from animal models. Connect Tissue Res. 1999;40:1-11.
18. Alsousou J, Thompson M, Hulley P, et al. The biology of platelet-rich plasma and its application in trauma and orthopaedic surgery: a review of the literature. J Bone Jt Surg. 2009;91:987-96.
19. Andıa I, Sanchez M, Maffullı N. Joint pathology and platelet-rich plasma therapies. Expert Opin Biol Ther. 2012;12:7-22.

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20. Gobbı A, Karnatzıkos G, Mahajan V, et al. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. Sports Health. 2012;4:162-72.

21. Fılardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol. Arthrosc. 2011;19:528-35.

22. Cerza F, Carnı S, Carcangıu A, et al. Comparison between hyaluronic acid and platelet-rich plasma, Intra-articular infiltration in the treatment of gonarthrosis. Am J Sports Med. 2012;40:2822-7.

23. Say F, Gürler D, Yener K, et al. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. Acta Chir Orthop Traumatol Cech. 2013;80:278-83.

24. Chen AL, Desai P, Adler EM, et al. Granulomatous inflammation after Hylan G-F 20 viscosupplementation of the knee: a report of six cases. J Bone Joint Surg. 2002;84-A:1142-7.

25. Weiss E. Knee osteoarthritis, body mass index and pain: data from the osteoarthritis initiative. Rheumatology (Oxford). 2014;53:2095-9.

26. Cubukcu D, Sarsan A, Alkan H. Relationships between pain, function and radiographic findings in osteoarthritis of the knee. A cross-sectional study. Arthritis. 2012;2012:984060.

27. Henderson B, Thompson RC, Hardingham T, et al. Inhibition of interleukin-1-induced synovitis and articular cartilage proteoglycan loss in the rabbit knee by recombinant human interleukin-1 receptor antagonist. Cytokine. 1991;3:246-9.

28. Caron JP, Fernandes JC, Martel-Pelletier J, et al. Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis. Suppression of collagenase-1 expression. Arthritis Rheum. 1996;39:1535-44.

29. Zhang P, Zhong ZH, Yu HT, et al. Exogenous expression of IL-1Ra and TGF-β1 promotes in vivo repair in experimental rabbit osteoarthritis. Scand J Rheumatol. 2015;44:404-11.

30. Wang F, Liu J, Chen X, et al. IL-1β receptor antagonist (IL-1Ra) combined with autophagy inducer (TAT-Beclin1) is an effective alternative for attenuating extracellular matrix degradation in rat and human osteoarthritis chondrocytes. Arthritis Res Ther. 2019;21:171.

31. Baltzer AWA, Moser C, Jansen SA, et al. Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthritis Cartilage. 2009;17:152-60.

32. Rutgers M, Saris DBF, Dhert WJA, et al. Cytokine profile of autologous conditioned serum for treatment of osteoarthritis, in vitro effects on cartilage metabolism and intra-articular levels after injection. Arthritis Res Ther. 2010;12:114.

33. Chevalier X, Goupille P, Beaulieu AD, et al. Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. 2009;61:344-52.

34. Auw Yang KG, Raijmakers NJH, Van Arkel ERA, et al. Autologous interleukin-1 receptor antagonist improves function and symptoms in osteoarthritis when compared to placebo in a prospective randomized controlled trial. Osteoarthritis Cartilage. 2008;16:498-505.

35. Vangsness T, Chung MH, Woodell-May J. Stimulation of IL-1ra production from platelet-rich plasma. 54th Annual Meeting of the Orthopaedic Research Society. San Francisco, USA. 2002.