World Journal of Orthopedics

Online Submissions: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
doi:10.5312/wjo.v5.i3.351

World J Orthop 2014 July 18; 5(3): 351-361
ISSN 2218-5836 (online)

REVIEW

Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis

Egemen Ayhan, Hayrettin Kesmezacar, Isik Akgun

Egemen Ayhan, Department of Orthopaedics and Traumatology, Mersin University, Mersin 33110, Turkey
Hayrettin Kesmezacar, Isik Akgun, Kaktus Health Center, Istanbul 34394, Turkey
Author contributions: Ayhan E, Kesmezacar H and Akgun I contributed to this paper for conception and design, acquisition of data, and interpretation of data, drafting the article and revising it critically for important intellectual content, and final approval of the version to be published.
Correspondence to: Egemen Ayhan, MD, Department of Orthopaedics and Traumatology, Mersin University, Mersin 33110, Turkey. egemenay@yahoo.com
Telephone: +90-532-6363693 Fax: +90-324-3374305
Received: December 29, 2013 Revised: March 9, 2014
Accepted: May 31, 2014
Published online: July 18, 2014

Abstract

Osteoarthritis (OA) is a complex "whole joint" disease pursued by inflammatory mediators, rather than purely a process of "wear and tear". Besides cartilage degradation, synovitis, subchondral bone remodeling, degeneration of ligaments and menisci, and hypertrophy of the joint capsule take parts in the pathogenesis. Pain is the hallmark symptom of OA, but the extent to which structural pathology in OA contributes to the pain experience is still not well known. For the knee OA, intraarticular (IA) injection (corticosteroids, viscosupplements, blood-derived products) is preferred as the last nonoperative modality, if the other conservative treatment modalities are ineffective. IA corticosteroid injections provide short term reduction in OA pain and can be considered as an adjunct to core treatment for the relief of moderate to severe pain in people with OA. IA hyaluronic acid (HA) injections might have efficacy and might provide pain reduction in mild OA of knee up to 24 wk. But for HA injections, the cost-effectiveness is an important concern that patients must be informed about the efficacy of these preparations. Although more high-quality evidence is needed, recent studies indicate that IA platelet rich plasma injections are promising for relieving pain, improving knee function and quality of life, especially in younger patients, and in mild OA cases. The current literature and our experience indicate that IA injections are safe and have positive effects for patient satisfaction. But, there is no data that any of the IA injections will cause osteophytes to regress or cartilage and meniscus to regenerate in patients with substantial and irreversible bone and cartilage damage.

Key words: Intraarticular injections; Corticosteroid; Hyaluronic acid; Platelet rich plasma; Knee osteoarthritis; Viscosupplementation

Core tip: Intraarticular (IA) corticosteroid injections can be considered as an adjunct to core treatment for short term reduction of moderate to severe pain in people with osteoarthritis (OA). IA hyaluronic acid (HA) injections might have efficacy and might provide pain reduction in mild OA of knee up to 24 wk. But for HA injections, the cost-effectiveness is an important concern that patients must be informed. Although more high-quality evidence is needed, recent studies indicate that IA platelet rich plasma injections are promising for relieving pain, improving knee function and quality of life, especially in younger patients, and in mild OA cases.

Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World J Orthop* 2014; 5(3): 351-361 Available from: URL: http://www.wjgnet.com/2218-5836/full/v5/i3/351.htm DOI: http://dx.doi.org/10.5312/wjo.v5.i3.351

INTRODUCTION

Osteoarthritis (OA) refers to a clinical syndrome of joint

pain with multifactorial etiopathogenesis that is characterized by the gradual loss of articular cartilage, osteophyte formation, subchondral bone remodeling, and inflammation of the joint[1]. OA is a major source of disability owing to pain and loss of function. It is the most common form of joint disease, and among the top 10 causes of disability worldwide[2]. With aging of the population and increasing obesity, OA arises as a major public health problem and an important financial burden for the global economy[3].

For the knee OA, various conservative treatment modalities are recommended by clinical guidelines[2,4,5]. The non-pharmacological modalities are patient education and self-management, exercises, weight reduction, walking supports (crutches), bracing, shoe and insoles modification, local cooling/heating, acupuncture, and electromagnetic therapy. Pharmacologic therapies can be summarized as paracetamol, non-steroidal anti-inflammatory drugs, opioids, and slow-acting drugs (glucosamine and chondroitin sulfate). If orally administered drugs are ineffective, intraarticular (IA) injection (corticosteroids, viscosupplements, blood-derived products) is the last nonoperative modality that can be preferred[5,6]. The major contraindication for IA injections is septic arthritis. In addition, in the presence of overlying soft tissue infection, there is risk of iatrogenic seeding to the joint.

When the various potential conservative treatment modalities and the uncertainty in regards to evidence-based recommendations are considered, it is inevitable that some inconsistencies exist between clinical guidelines[2,4,5]. However, the consensus occurs in two points: (1) The optimal conservative management of knee OA requires a combination of pharmacological and non-pharmacological treatment modalities customized to individual patient needs; and (2) The main goals of conservative management are to reduce pain, improve function and quality of life, and limit disease progression.

Etiopathogenesis of OA

To refer OA as "degenerative joint disease" would be a misnomer because OA is not simply a process of "wear and tear" but rather a much more complex disease driven by inflammatory mediators within the affected joint[7-11]. Recent researches supports that, OA is a "whole joint" disease[7-9]. Although cartilage destruction is the hallmark of the disease; synovitis, subchondral bone remodeling (thickening, bone collapse, bone cysts), degeneration of ligaments and menisci, and hypertrophy of the joint capsule take parts in the pathogenesis of OA[1].

The loss of articular cartilage is probably initiated as a focal lesion, which may progressively extend and produce changes in loading, thereby increasing loss of cartilage. This pathoanatomical description of cartilage loss process involves morphologic and metabolic changes in chondrocytes, as well as biochemical and structural alterations in the ECM, under the influence of complex mechanical, biological, biochemical, molecular, and enzymatic feedback loops[1]. In OA, chondrocytes, which are responsive to mechanical (*e.g.*, malalignment, articular cartilage incongruity, …) and inflammatory stimulation, become activated to produce inflammatory mediators, similar to an injury response[8,12]. Also, subchondral bone cells response in a similar way, and may take role in degradation of the deep layer of cartilage[13]. As articular cartilage matrix proteins are fragmented, these fragments feedback and stimulate further matrix destruction[8]. On the other hand, aging-related changes in chondrocytes (*i.e.,* accumulation of advanced glycation end-products) make the cartilage more brittle and lead to increased production of cytokines and chemokines by aged chondrocytes[14]. Therefore, increased age also arises as an important risk factor for OA.

Synovial inflammation plays a critical role in the symptoms and structural progression of OA. Soluble inflammatory mediators, such as cytokines and chemokines, are increased in synovial fluid (SF) in OA and promote synovitis[8]. Recent histological researches demonstrated that synovitis occurs even in early stages of disease, but the prevalence of synovitis increases with advancing disease stage[15,16]. The cause of synovial inflammation in OA is still unclear but hypothesized either as a result of foreign body reaction of synovial cells to degraded cartilage products inside the joint, or as a primary trigger of OA process[7,8,17,18]. Whatsoever, synovial cells are thought to produce inflammatory mediators, activate chondrocytes, and propagate cartilage breakdown[7]. Supporting this, synovitis has been shown to correlate with symptom severity and rate of cartilage degeneration[9,18-20].

Inflammatory mediators play a pivotal role in the initiation and continuation of the OA process. The source of such mediators may be local from joint cells, as previously mentioned, but also may be systemic from other tissues such as adipose tissue (*i.e.*, adipokine) released in blood flow and then reaching the joint via the subchondral bone vasculature[7,21]. The risk of hand OA is increased two-fold in obese patients[22]. This finding explains the theory of obesity as a risk factor for OA; not only because of mechanical overload, but also because of systemic factors. It was reported that adipokines, secreted mainly from abdominal adipose tissue, contribute to the low-grade inflammatory state of obese patients and may directly affect cartilage homeostasis[10,21].

Currently, it has become evident that the inflammatory mediators contribute significantly to the development and progression of structural changes in the OA joint. Because the induction of proinflammatory mediators in cartilage, synovial membrane, and subchondral bone and their signaling pathways are interlinked and overlapped, it therefore remains controversial whether inflammatory mediators are primary or secondary regulators of cartilage damage and defective repair mechanisms in OA[10]. Nevertheless, compounds that regulate cytokine synthesis or activity, or both, are considered as favorable targets for future OA therapy[11].

Pain

The hallmark symptom of OA is pain. The early stages

of OA is characterized by activity related pain, thereafter, with the advancing disease, the pain gets the chronicity character and converts to a more constant nature with accompanying intense pain attacks[3]. Genetic predisposition was associated with development of chronic pain in knee OA[23]. Weight has been shown as a potential factor contributing not only to OA risk, but also to pain[24].

Adult articular cartilage is avascular and aneural, so that cartilage is incapable of directly generating pain or inflammation, at least early in the disease course prior to potential neurovascular invasion that may occur in late or end-stage disease[25,26]. Pathologic changes to non-cartilaginous joint tissues are of particular interest in understanding the source of pain generation in OA. The subchondral bone, synovium, joint capsule, periarticular ligaments, and periarticular muscle are all richly innervated and are the likely source of pain in OA[25].

During inflammation or cartilage degradation, inflammatory mediators are released and sensitize primary afferent nerves. Thereby, the subchondral bone and pain receptors are exposed because of stripped cartilage, and there appears vascular congestion of subchondral bone which increases intraosseous pressure. Walsh *et al*[27] have observed sensory nerve fibers in the vascular channels associated with osteochondral angiogenesis and speculated that they could be a potential source of symptomatic pain.

Synovitis and effusion is frequently present in OA and correlates with pain and other clinical outcomes[28,29]. Synovial causes of pain include stimulation of nociceptors within the synovium from osteophytes and inflammation[30]. Histologically, the infiltrations of macrophages and lymphocytes, and villous hyperplasia in advanced disease, are observed in synovitis with knee OA[31]. Recently, an increase in vascularity accompanied by increased sensory nerves has been noted also in OA menisci, which may relate the otherwise painless menisci, as a source of pain in knee OA[32]. In a recent review, Mapp *et al*[33] emphasized that during OA, angiogenesis is increased in the synovium, osteophytes and menisci and leads to ossification in osteophytes and the deep layers of articular cartilage. The authors concluded that angiogenesis contribute to structural damage and pain in OA, and they suggested the angiogenesis as a potential target for new treatments. Finally, impairments in periarticular muscle function affect joint loading and arises as a source of pain in people with OA[34].

In conclusion, although the relationship of changes in bone marrow lesions and in synovitis with fluctuation in pain presence and severity were demonstrated in the study of Zhang *et al*[35], the extent to which structural pathology in OA contributes to the pain experience is still not well known, this is probably because of co-existence of the structural pathologies and variations in personal pain perception[36]. On the other hand, angiogenesis arises as a reasonable target for future treatment modalities in OA.

CORTICOSTEROID INJECTION

Agents

There are 5 injectable corticosteroids that have a current Food and Drug Administration (FDA) label for IA injections. These consist of methylprednisolone acetate, triamcinolone acetate, betamethasone acetate and betamethasone sodium phosphate, triamcinolone hexacetonide, and dexamethasone.

A few trials have been published comparing functional outcomes after different IA corticosteroid (CS) injections[37-39]. However, the results were inconclusive. Although, further research is needed, it seems that any agent have similar potency provided with correct indication, dosage, timing, and application[40].

Mechanism of action

Corticosteroids have both anti-inflammatory and immunosuppressive effect, but their mechanism of action is complex. Corticosteroids act directly on nuclear steroid receptors and interrupt the inflammatory and immune cascade at several levels. By this means, they reduce vascular permeability and inhibit accumulation of inflammatory cells, phagocytosis, production of neutrophil superoxide, metalloprotease, and metalloprotease activator, and prevent the synthesis and secretion of several inflammatory mediators such as prostaglandin and leukotrienes[41,42]. The clinical anti-inflammatory reflections of these actions are decreases in erythema, swelling, heat, and tenderness of the inflamed joints and an increase in relative viscosity with an increase in hyaluronic acid (HA) concentration[41,43].

Indications and efficacy

IA CS injections are frequently used to treat acute and chronic inflammatory conditions. Especially during the OA flare, when there is evidence of inflammation and joint effusion, CS injections decrease acute episodes of pain and increase joint mobility[44]. Also, when the correlation of chondrolysis with the OA flare is considered, the IA CS injection for the short-term treatment of disease flares is recommended[9,18-20].

From randomized controlled trials in OA patients there is evidence that IA corticosteroids are effective, but their benefit over placebo may be relatively short-lived, up to four weeks. In a 2006 Cochrane Review, the short term efficacy of corticosteroids in knee OA has been confirmed[45], and recently, the short-term effect was also highlighted in a systematic review by Hepper *et al*[46] and in a meta-analysis by Bannuru *et al*[47]. One more recent study also found IA corticosteroids to be superior to placebo on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total subscale scores at four weeks[48]. Moreover, some studies suggest a possible benefit of up to 26 wk[49,50]. On the other hand, in the 2006 Cochrane Review, it was also stated that there was a lack of evidence for efficacy in functional improvement

(*e.g.*, stiffness, walking distance, quality of life) at any time point with IA CS injections[45].

The clinical predictors for IA CS injection efficacy were studied. In 1995, Gaffney *et al*[51] reported that joint effusion and successful aspiration of SF at the time of CS injection were related with better pain reduction at one week. Promoting this study, in a more recent research, Arden *et al*[50] concluded that presence of an effusion and a lesser radiographic severity of knee OA are predictors of a good response to treatment with CS injections up to 26 wk. However, in a very recent systematic review about clinical predictors of response to IA CS injection in knee OA, no consistent predictors of response were identified[52]. The authors concluded that predictor factors were poorly studied in previous trials, which may be partly the cause of this result.

IA injection of CS has rare side effects. The infrequent reactive flares to IA administration may begin 6–12 h after injection and resolve spontaneously in 1 to 3 d[53]. Early studies in rodents reported the possibility of cartilage destruction[54-56]. However, subsequent studies showed that even multiple IA injections of steroids showed no significant evidence of knee cartilage degradation[57-59].

The American College of Rheumatology subcommittee on OA recommends CS injections as an effective method of decreasing pain[60]. However, American Society of Orthopedic Surgeons work group interpreted the evidence to be inconclusive as to the benefit of IA corticosteroids and were unable to recommend for or against the use of IA corticosteroids in their guideline for patients with symptomatic OA of the knee[4].

To sum up, the research evidence demonstrates that IA CS injections provide short term reduction in OA pain and can be considered as an adjunct to core treatment for the relief of moderate to severe pain in people with OA[2].

HYALURONIC ACID INJECTION (VISCOSUPPLEMENTATION)

Agents

HA is produced either from harvested rooster combs or via bacterial fermentation in vitro[61]. The injectable hyaluronan products that are approved by FDA are sodium hyaluronate, Hylan G-F 20, and high-molecular-weight hyaluronan. Injection schedules vary from 1 to 5 injections and patients are generally advised to repeat the injection schedule by 6 mo if they are satisfied with the previous injection course.

Although the basic science evidence studies seem to suggest that the use of both low molecular weight hyaluronic acid and high molecular weight hyaluronic acid (HMWHA) have disease modifying effects, comparative clinical studies and meta-analyses tends to favor the efficacy of HMWHA for knee OA[62-66]. Nevertheless, the current literature is inconclusive because of heterogeneity of studies[63-65,67].

Mechanism of action

HA is a naturally occurring glycosaminoglycan and a component of SF and cartilage matrix. Synovial cells, fibroblasts and chondrocytes synthesize HA and secrete into the joint. HA enhances viscosity and elastic nature of SF. SF with normal HA concentration acts as a viscous lubricant during slow joint movements and as an elastic shock absorber during rapid joint movements[68]. The adaptive ability reduces stress and friction on cartilage[69]. It also forms the backbone for the proteoglycans of the extracellular matrix. HA functions through anti-inflammatory, anabolic, analgesic, and chondroprotective mechanisms[70]. In the osteoarthritic joint, synovial inflammation leads to increased permeability of the synovial membrane for HA. Also, the elevated SF levels of free radicals, inflammatory cytokines, and proteolytic enzymes in osteoarthritic knees impair HA function and contribute to the progression of OA[71,72]. Therefore in OA, both the molecular weight and the concentration of HA are decreased[71-74].

The IA injection of HA is thought to restore normal viscoelastic properties of the pathologically altered SF, which explains the term of the approach: "viscosupplementation"[71]. It is thought that HA temporarily restores the lubricating and shock-absorbing effects of SF. Moreover, several studies suggest that viscosupplements also have disease modifying effects, such as reduction of synovial inflammation[67,75-79], protection against cartilage erosion[80,81], and promotion of IA HA production[62,74,82,83]. Although the precise in vivo mechanisms of action are poorly known in the joint, HA promotes tissue remodeling in other tissues, as well. It is used to optimize tissue restoration and minimize scarring in ophthalmic, thoracic and plastic surgery[84,85], and is also used to prevent postoperative peritoneal and intrauterine adhesions[86,87]. Lastly, HA have indirect and direct analgesic activity within the joints. Indirect effect is via the anti-inflammatory properties of HA. Direct effect is by the direct inhibition of nociceptors and the decreased synthesis of bradykinin and substance P[74,82,83,88].

Indications and efficacy

Viscosupplementation is widely applied to improve biomechanical function by replacing the reduced HA of osteoarthritic knee and pain management based on potentially therapeutic physicochemical properties[71,74,89].

However, despite many clinical trials, the efficacy of HA is a matter of debate with markedly discordant interpretations of the data[90]. Among the published meta-analyses, two concluded an overall beneficial effect for HA injections[63,91], four reported a small benefit[66,90,92,93], and two found no evidence to support HA injection therapy for knee OA[94,95]. Rutjes *et al*[96] found overall no clinically important benefit for pain intensity or frequency of OA flares in 89 trials involving 12667 patients. On the other hand, Bannuru *et al*[90] reported that HA asserts modest positive effect for certain clinical situations up to 24 wk, but its cost-effectiveness is advised to be re-

evaluated. Supporting this, National Health Service in Wales and England (NHS) reported in their guideline for management of OA that despite the evidence seems to suggest a benefit for reducing pain up to three months after a series of three to five injections, the cost-effectiveness estimate of HA injections is outside the realms of affordability[2].

When reviewed individually, most trials reported positive effects of HA, but there were considerable heterogeneity in the clinical research methodology[6,66,77]. Populations with variable OA severity, variable inclusion, exclusion and assessment criteria, different molecular weights of HA, different injection schedules were included in the trials. Also, there exists the potential for publication bias and the differences about interpretation of the clinical importance of the observed treatment effects[66].

In a very recent review, Printz *et al*[97] investigated financial conflicts of interest in studies on the therapeutic effects of IA HA injections for treatment of knee OA. The results demonstrated that 63% of studies were industry funded. None of the studies with at least one company employee as an author reported an unfavorable conclusion about the efficacy of HA in the treatment of knee OA. The authors concluded that the conclusions in studies on HA injections for knee OA were commonly associated with industry authorship. The authors advised the clinicians to be aware of the potential financial conflicts of interest of the authors reporting on this topic and carefully evaluate the recommendations from these studies based on the objectivity of the study design.

IA injection of HA is safe for use in patients with knee OA[66,98]. The only adverse effects of significance are transient local reactions in the injected joint observed at a rate of 2% to 4%[89,99,100].

The American College of Rheumatology subcommittee on OA has no recommendations regarding the use of IA hyaluronates[60]. However, American Society of Orthopedic Surgeons does not recommend using IA HA for patients with symptomatic OA of the knee. Work group interpreted the quality of the supporting evidence is high and the strength of recommendation is strong against the use of IA HA in their guideline[4].

To sum up, the research evidence demonstrates that IA HA injections are safe and might have efficacy and might provide pain reduction in mild OA of knee up to 24 weeks. But, the cost-effectiveness is an important concern that patients must be informed about the efficacy of these preparations. Therefore, beside patient expectations, cost-effectivity must be considered before deciding on this treatment.

PLATELET RICH PLASMA

Agents

Platelet rich plasma (PRP) is prepared from autologous blood by centrifugation to obtain a highly concentrated sample of platelets, which is four to five times higher than that of normal blood[101]. The platelets undergo degranulation to release growth factors (GFs). The plasma is the acellular portion of mixture including cytokines, thrombin, and other GFs.

Different preparation methods for PRP can yield products with different compositions and characteristics. Dohan Ehrenfest *et al*[102] described three methods of producing PRP: (1) the double-spinning method, that yields a four to eight fold change in platelet concentration over baseline levels and also concentrates leucocytes; (2) the single-spinning method, that yields a one- to three fold change in platelet concentration over baseline levels; and (3) selective blood filtration. Based on their leukocyte and fibrin content, different PRP formulations are such as: pure PRP, leukocyte-rich PRP, pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin[102]. Although some data show better results with PRP formulations with leucocyte depletion, the superiority of one PRP formulation over another for clinical effectiveness has not been established[103].

Mechanism of action

The platelet concentrate is activated by addition of calcium chloride, and this results in the formation of platelet gel and the release of growth factors and bioactive molecules[104]. Thereby, platelets actively participate in healing processes by delivering a broad spectrum of GFs (insulin-like growth factor, transforming growth factor b-I, platelet derived growth factor, and many others) and other active molecules (*e.g.*, cytokines, chemokines, arachidonic acid metabolites, extracellular matrix proteins, nucleotides, ascorbic acid) to the injured site[105]. These factors altogether contribute to comprehensive roles of PRP, including chondrogenesis, bone remodeling, proliferation, angiogenesis, antiinflammation, coagulation and cell differentiation[106,107].

In experimental studies on animal models with OA, PRP was related with decreased chondrocyte apoptosis, increased proteoglycans in the articular cartilage, and prevention against OA progression[108-114]. The effects were related to severity of OA[112]. However, PRP formulations are complex, and many of the questions about PRP mechanisms of action in a joint with OA remain unanswered[103,115]. In a recent review, Andia *et al*[116] concluded that although the effectors mediating the beneficial effects of PRPs have not been identified and research is complex because platelets contain more than 300 proteins, this therapy could act as an endogenous source of chondroprotection by interfering with the early catabolic and inflammatory events and by subsequently promoting anabolic responses.

Indications and efficacy

PRP is a blood product that allows in a simple, low cost, and minimally invasive way to obtain a concentration of many of growth factors and biologically active molecules and its use is associated with reduced inflammation, pain relief, improved function, and possible cartilage regeneration. The major problem is mechanisms underlying this

potential therapeutic effect of PRP remain poorly understood. Furthermore, interpatient variability and the lack of biochemical and imaging biomarkers to improve diagnosis specificity of OA make demarcating PRP therapies difficult. Therefore, strong evidence from well-designed clinical trials to support PRP therapy for OA of the knee is needed[115].

Sánchez *et al*[117] was first to describe the IA injection of plasma rich in growth factors to treat an articular cartilage avulsion in a soccer player. Next, in a retrospective study, the similar study group reported preliminary results of an autologous preparation rich in growth factors injection for knee OA, suggesting the safety and usefulness of this treatment approach[118]. Sampson *et al*[119] performed three sets of IA PRP injections at four weeks intervals for 14 patients affected by knee OA and reported a favorable outcome in most of the patients at 12 mo of follow-up. Kon *et al*[120] performed three sets of IA PRP injections at 21-d intervals to 115 osteoarthritic knees, and reported significant improvement at 6- and 12-mo of follow-up. However, they reported a worsening of the results after 6 mo of follow-up, even if still significantly was higher by the 12th-month with respect to the basal level. The similar study group performed a 2 year's follow-up evaluation and although they observed an overall worsening of the results, the results still showed improved quality of life for the patients[121]. In this study, the results showed 9 mo of median duration of the beneficial effects and were better in young patients with lower degrees of OA. Similar results were confirmed in recent studies[122-128].

In clinical studies to date, PRP is safe, with no serious complications reported. Minor adverse events associated with repeated IA injections have been moderate pain, swelling and mild effusion that lasted a few days[121,122,125-127,129].

American Society of Orthopedic Surgeons work group interpreted the evidence to be inconclusive as to the benefit of IA PRP injection and were unable to recommend for or against the use of IA PRP injection in their guideline for patients with symptomatic OA of the knee[4].

To sum up, studies indicate that PRP is promising for relieving pain, improving knee function and quality of life[115,119,121,128,130]. But, there is no data that PRP will cause osteophytes to regress or cartilage and meniscus to regenerate in patients with substantial and irreversible bone and cartilage damage. More promising results are shown in younger patients, and in mild OA cases. Despite the interesting preliminary findings and the increasing clinical application of this attractive treatment approach, extensive clinical use of PRP in OA is not supported by high-quality evidence of a clear clinical improvement[6]. But its low cost, the simple preparation technique, safety, and biologically active content have led to high acceptance both by patients and physicians.

Comparative studies

In the Cochrane reviews of trials comparing IA HA injections with IA corticosteroids, there were no significant differences 4 wk after injection but IA HA was shown to be more effective 5-13 wk post injection[45,91]. This is further supported by a meta-analysis of seven randomized controlled trials in patients with knee OA in which IA HA was compared directly with IA CS[47]. In the first two weeks, corticosteroids were more effective in relieving pain, but at week 4, both were equally effective, and from week 8, HA was more effective to last assessment at 26th week. Analyses of the results for other outcomes such as reduction in stiffness and improvement in function following IA HA were similar.

In the recent studies comparing PRP and HA, Kon *et al*[122] studied PRP versus HA injections in 150 patients, with PRP treatment giving better results than HA in reducing pain and symptoms and recovering articular function up to 6 mo. In this study, PRP showed a better performance compared with HA in younger patients affected by cartilage lesions or early OA. However, PRP and HA treatments offered similar results in patients aged over 50 years and in the treatment of advanced OA. Also, Spakova *et al*[129] compared 120 patients receiving IA injection of either HA or PRP. The authors reported that statistically significantly better results in the scores were recorded in a group of patients who received PRP injections after a 3- and 6-mo of follow-up. Say *et al*[131], compared IA HA and PRP injections in their prospective study and concluded that the application of single dose PRP to be a safe, effective and low-cost method for treating OA. Finally, in very recent three Level 1 studies, two randomized HA controlled clinical trials[125,126] and one placebo-controlled trial[127], PRP decreased pain and improved function in all three trials better than HA or placebo.

CONCLUSION

The current literature and our experience indicate that IA injections are safe and have positive effects for patient satisfaction. But, we are not sure that what ratio of this worthy outcome derives either from the real disease modifying effect or from the placebo effect of these drugs. When the unclear etiopathogenesis and the heterogeneity of OA are considered, it is hard to categorize the patients and their level of disease for IA injection choice. In regards to our experience, patient characteristics, symptoms, and clinical findings may indicate a practical approach for IA injections. The CS choice is reasonable in acute and persistent synovitis for patients that cannot be operated. The corticosteroids are effective in short-term. We prefer HA for obese patients who are older than 60 years and for patients with extremity malalignment. The supposed long-term effect of HA is attractive for these patients who are not willing to be operated. We prefer PRP for patients who are younger than 60 years, with mild OA and body mass index < 30, and for patients that do not have any extremity malalignment. If the patients are older than 60 years, or their body mass index > 30,

or they have moderate OA, we still apply PRP injection, which is followed by a supplementary single dose of HA injection 2 to 4 wk after PRP injection.

REFERENCES

1 **Martel-Pelletier J**, Boileau C, Pelletier JP, Roughley PJ. Cartilage in normal and osteoarthritis conditions. *Best Pract Res Clin Rheumatol* 2008; **22**: 351-384 [PMID: 18455690 DOI: 10.1016/j.berh.2008.02.001]

2 **National Collaborating Centre for Chronic Conditions (UK).** Osteoarthritis: National clinical guideline for care and management in adults. London: Royal College of Physicians (UK), 2008

3 **Neogi T**. The epidemiology and impact of pain in osteoarthritis. *Osteoarthritis Cartilage* 2013; **21**: 1145-1153 [PMID: 23973124 DOI: 10.1016/j.joca.2013.03.018]

4 **Jevsevar DS**, Brown GA, Jones DL, Matzkin EG, Manner PA, Mooar P, Schousboe JT, Stovitz S, Sanders JO, Bozic KJ, Goldberg MJ, Martin WR, Cummins DS, Donnelly P, Woznica A, Gross L. The American Academy of Orthopaedic Surgeons evidence-based guideline on: treatment of osteoarthritis of the knee, 2nd edition. *J Bone Joint Surg Am* 2013; **95**: 1885-1886 [PMID: 24288804]

5 **Zhang W**, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. *Osteoarthritis Cartilage* 2010; **18**: 476-499 [PMID: 20170770 DOI: 10.1016/j.joca.2010.01.013]

6 **Kon E**, Filardo G, Drobnic M, Madry H, Jelic M, van Dijk N, Della Villa S. Non-surgical management of early knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2012; **20**: 436-449 [PMID: 22037809 DOI: 10.1007/s00167-011-1713-8]

7 **Berenbaum F**. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis Cartilage* 2013; **21**: 16-21 [PMID: 23194896 DOI: 10.1016/j.joca.2012.11.012]

8 **Loeser RF**, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. *Arthritis Rheum* 2012; **64**: 1697-1707 [PMID: 22392533 DOI: 10.1002/art.34453]

9 **Scanzello CR**, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. *Bone* 2012; **51**: 249-257 [PMID: 22387238 DOI: 10.1016/j.bone.2012.02.012]

10 **Goldring MB**, Otero M. Inflammation in osteoarthritis. *Curr Opin Rheumatol* 2011; **23**: 471-478 [PMID: 21788902 DOI: 10.1097/BOR.0b013e328349c2b1]

11 **Kapoor M**, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. *Nat Rev Rheumatol* 2011; **7**: 33-42 [PMID: 21119608 DOI: 10.1038/nrrheum.2010.196]

12 **Guilak F**. Biomechanical factors in osteoarthritis. *Best Pract Res Clin Rheumatol* 2011; **25**: 815-823 [PMID: 22265263 DOI: 10.1016/j.berh.2011.11.013]

13 **Sanchez C**, Pesesse L, Gabay O, Delcour JP, Msika P, Baudouin C, Henrotin YE. Regulation of subchondral bone osteoblast metabolism by cyclic compression. *Arthritis Rheum* 2012; **64**: 1193-1203 [PMID: 22034083 DOI: 10.1002/art.33445]

14 **Loeser RF**. Aging and osteoarthritis: the role of chondrocyte senescence and aging changes in the cartilage matrix. *Osteoarthritis Cartilage* 2009; **17**: 971-979 [PMID: 19303469 DOI: 10.1016/j.joca.2009.03.002]

15 **Benito MJ**, Veale DJ, FitzGerald O, van den Berg WB, Bresnihan B. Synovial tissue inflammation in early and late osteoarthritis. *Ann Rheum Dis* 2005; **64**: 1263-1267 [PMID: 15731292]

16 **Krasnokutsky S**, Belitskaya-Lévy I, Bencardino J, Samuels J, Attur M, Regatte R, Rosenthal P, Greenberg J, Schweitzer M, Abramson SB, Rybak L. Quantitative magnetic resonance imaging evidence of synovial proliferation is associated with radiographic severity of knee osteoarthritis. *Arthritis Rheum* 2011; **63**: 2983-2991 [PMID: 21647860 DOI: 10.1002/art.30471]

17 **Sellam J**, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. *Nat Rev Rheumatol* 2010; **6**: 625-635 [PMID: 20924410 DOI: 10.1038/nrrheum.2010.159]

18 **Ayral X**, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis -- results of a 1 year longitudinal arthroscopic study in 422 patients. *Osteoarthritis Cartilage* 2005; **13**: 361-367 [PMID: 15882559]

19 **Roemer FW**, Guermazi A, Felson DT, Niu J, Nevitt MC, Crema MD, Lynch JA, Lewis CE, Torner J, Zhang Y. Presence of MRI-detected joint effusion and synovitis increases the risk of cartilage loss in knees without osteoarthritis at 30-month follow-up: the MOST study. *Ann Rheum Dis* 2011; **70**: 1804-1809 [PMID: 21791448 DOI: 10.1136/ard.2011.150243]

20 **Conaghan PG**, D'Agostino MA, Le Bars M, Baron G, Schmidely N, Wakefield R, Ravaud P, Grassi W, Martin-Mola E, So A, Backhaus M, Malaise M, Emery P, Dougados M. Clinical and ultrasonographic predictors of joint replacement for knee osteoarthritis: results from a large, 3-year, prospective EULAR study. *Ann Rheum Dis* 2010; **69**: 644-647 [PMID: 19433410 DOI: 10.1136/ard.2008.099564]

21 **Pottie P**, Presle N, Terlain B, Netter P, Mainard D, Berenbaum F. Obesity and osteoarthritis: more complex than predicted! *Ann Rheum Dis* 2006; **65**: 1403-1405 [PMID: 17038451]

22 **Yusuf E**, Nelissen RG, Ioan-Facsinay A, Stojanovic-Susulic V, DeGroot J, van Osch G, Middeldorp S, Huizinga TW, Kloppenburg M. Association between weight or body mass index and hand osteoarthritis: a systematic review. *Ann Rheum Dis* 2010; **69**: 761-765 [PMID: 19487215 DOI: 10.1136/ard.2008.106930]

23 **Malfait AM**, Seymour AB, Gao F, Tortorella MD, Le Graverand-Gastineau MP, Wood LS, Doherty M, Doherty S, Zhang W, Arden NK, Vaughn FL, Leaverton PE, Spector TD, Hart DJ, Maciewicz RA, Muir KR, Das R, Sorge RE, Sotocinal SG, Schorscher-Petcu A, Valdes AM, Mogil JS. A role for PACE4 in osteoarthritis pain: evidence from human genetic association and null mutant phenotype. *Ann Rheum Dis* 2012; **71**: 1042-1048 [PMID: 22440827 DOI: 10.1136/annrheumdis-2011-200300]

24 **Richette P**, Poitou C, Garnero P, Vicaut E, Bouillot JL, Lacorte JM, Basdevant A, Clément K, Bardin T, Chevalier X. Benefits of massive weight loss on symptoms, systemic inflammation and cartilage turnover in obese patients with knee osteoarthritis. *Ann Rheum Dis* 2011; **70**: 139-144 [PMID: 20980288 DOI: 10.1136/ard.2010.134015]

25 **Felson DT**. The sources of pain in knee osteoarthritis. *Curr Opin Rheumatol* 2005; **17**: 624-628 [PMID: 16093843]

26 **Suri S**, Gill SE, Massena de Camin S, Wilson D, McWilliams DF, Walsh DA. Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Ann Rheum Dis* 2007; **66**: 1423-1428 [PMID: 17446239]

27 **Walsh DA**, McWilliams DF, Turley MJ, Dixon MR, Fransès RE, Mapp PI, Wilson D. Angiogenesis and nerve growth factor at the osteochondral junction in rheumatoid arthritis and osteoarthritis. *Rheumatology* (Oxford) 2010; **49**: 1852-1861 [PMID: 20581375 DOI: 10.1093/rheumatology/keq188]

28 **Hill CL**, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H, Gale D, Grainger A, Conaghan P, Felson DT. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Ann Rheum Dis*

2007; **66**: 1599-1603 [PMID: 17491096]
29 **Baker K**, Grainger A, Niu J, Clancy M, Guermazi A, Crema M, Hughes L, Buckwalter J, Wooley A, Nevitt M, Felson DT. Relation of synovitis to knee pain using contrast-enhanced MRIs. *Ann Rheum Dis* 2010; **69**: 1779-1783 [PMID: 20472593 DOI: 10.1136/ard.2009.121426]
30 **Hunter DJ**, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. *Rheum Dis Clin North Am* 2008; **34**: 623-643 [PMID: 18687276 DOI: 10.1016/j.rdc.2008.05.004]
31 **Pearle AD**, Scanzello CR, George S, Mandl LA, DiCarlo EF, Peterson M, Sculco TP, Crow MK. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthritis Cartilage* 2007; **15**: 516-523 [PMID: 17157039]
32 **Ashraf S**, Wibberley H, Mapp PI, Hill R, Wilson D, Walsh DA. Increased vascular penetration and nerve growth in the meniscus: a potential source of pain in osteoarthritis. *Ann Rheum Dis* 2011; **70**: 523-529 [PMID: 21081524 DOI: 10.1136/ard.2010.137844]
33 **Mapp PI**, Walsh DA. Mechanisms and targets of angiogenesis and nerve growth in osteoarthritis. *Nat Rev Rheumatol* 2012; **8**: 390-398 [PMID: 22641138 DOI: 10.1038/nrrheum.2012.80]
34 **Hurley MV**. The role of muscle weakness in the pathogenesis of osteoarthritis. *Rheum Dis Clin North Am* 1999; **25**: 283-298, vi [PMID: 10356418]
35 **Zhang Y**, Nevitt M, Niu J, Lewis C, Torner J, Guermazi A, Roemer F, McCulloch C, Felson DT. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. *Arthritis Rheum* 2011; **63**: 691-699 [PMID: 21360498 DOI: 10.1002/art.30148]
36 **Hunter DJ**, Guermazi A, Roemer F, Zhang Y, Neogi T. Structural correlates of pain in joints with osteoarthritis. *Osteoarthritis Cartilage* 2013; **21**: 1170-1178 [PMID: 23973127 DOI: 10.1016/j.joca.2013.05.017]
37 **Valtonen EJ**. Clinical comparison of triamcinolonehexacetonide and betamethasone in the treatment of osteoarthrosis of the knee-joint. *Scand J Rheumatol Suppl* 1981; **41**: 1-7 [PMID: 6765509]
38 **Pyne D**, Ioannou Y, Mootoo R, Bhanji A. Intra-articular steroids in knee osteoarthritis: a comparative study of triamcinolone hexacetonide and methylprednisolone acetate. *Clin Rheumatol* 2004; **23**: 116-120 [PMID: 15045624]
39 **Yavuz U**, Sökücü S, Albayrak A, Oztürk K. Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. *Rheumatol Int* 2012; **32**: 3391-3396 [PMID: 22057944 DOI: 10.1007/s00296-011-2188-0]
40 **Schumacher HR**, Chen LX. Injectable corticosteroids in treatment of arthritis of the knee. *Am J Med* 2005; **118**: 1208-1214 [PMID: 16271901]
41 **Ostergaard M**, Halberg P. Intra-articular corticosteroids in arthritic disease: a guide to treatment. *BioDrugs* 1998; **9**: 95-103 [PMID: 18020548]
42 **Creamer P**. Intra-articular corticosteroid treatment in osteoarthritis. *Curr Opin Rheumatol* 1999; **11**: 417-421 [PMID: 10503664]
43 **JESSAR RA**, GANZELL MA, RAGAN C. The action of hydrocortisone in synovial inflammation. *J Clin Invest* 1953; **32**: 480-482 [PMID: 13052711]
44 **Rozental TD**, Sculco TP. Intra-articular corticosteroids: an updated overview. *Am J Orthop* (Belle Mead NJ) 2000; **29**: 18-23 [PMID: 10647515]
45 **Bellamy N**, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006; **(2)**: CD005328 [PMID: 16625636]
46 **Hepper CT**, Halvorson JJ, Duncan ST, Gregory AJ, Dunn WR, Spindler KP. The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies. *J Am Acad Orthop Surg* 2009; **17**: 638-646 [PMID: 19794221]
47 **Bannuru RR**, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum* 2009; **61**: 1704-1711 [PMID: 19950318 DOI: 10.1002/art.24925]
48 **Chao J**, Wu C, Sun B, Hose MK, Quan A, Hughes TH, Boyle D, Kalunian KC. Inflammatory characteristics on ultrasound predict poorer longterm response to intraarticular corticosteroid injections in knee osteoarthritis. *J Rheumatol* 2010; **37**: 650-655 [PMID: 20080918 DOI: 10.3899/jrheum.090575]
49 **Arroll B**, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. *BMJ* 2004; **328**: 869 [PMID: 15039276]
50 **Arden NK**, Reading IC, Jordan KM, Thomas L, Platten H, Hassan A, Ledingham J. A randomised controlled trial of tidal irrigation vs corticosteroid injection in knee osteoarthritis: the KIVIS Study. *Osteoarthritis Cartilage* 2008; **16**: 733-739 [PMID: 18077189]
51 **Gaffney K**, Ledingham J, Perry JD. Intra-articular triamcinolone hexacetonide in knee osteoarthritis: factors influencing the clinical response. *Ann Rheum Dis* 1995; **54**: 379-381 [PMID: 7794044]
52 **Maricar N**, Callaghan MJ, Felson DT, O'Neill TW. Predictors of response to intra-articular steroid injections in knee osteoarthritis--a systematic review. *Rheumatology* (Oxford) 2013; **52**: 1022-1032 [PMID: 23264554 DOI: 10.1093/rheumatology/kes368]
53 **Gerwin N**, Hops C, Lucke A. Intraarticular drug delivery in osteoarthritis. *Adv Drug Deliv Rev* 2006; **58**: 226-242 [PMID: 16574267]
54 **CHANDLER GN**, WRIGHT V. Deleterious effect of intra-articular hydrocortisone. *Lancet* 1958; **2**: 661-663 [PMID: 13588963]
55 **Meyer WL**, Kunin AS. Decreased glycolytic enzyme activity in epiphyseal cartilage of cortisone-treated rats. *Arch Biochem Biophys* 1969; **129**: 431-437 [PMID: 4304211]
56 **Mankin HJ**, Conger KA. The acute effects of intra-articular hydrocortisone on articular cartilage in rabbits. *J Bone Joint Surg Am* 1966; **48**: 1383-1388 [PMID: 5921793]
57 **Balch HW**, Gibson JM, El-Ghobarey AF, Bain LS, Lynch MP. Repeated corticosteroid injections into knee joints. *Rheumatol Rehabil* 1977; **16**: 137-140 [PMID: 910089]
58 **Keagy RD**, Keim HA. Intra-articular steroid therapy: repeated use in patients with chronic arthritis. *Am J Med Sci* 1967; **253**: 45-51 [PMID: 6017017]
59 **Ayral X**. Injections in the treatment of osteoarthritis. *Best Pract Res Clin Rheumatol* 2001; **15**: 609-626 [PMID: 11567543]
60 **Hochberg MC**, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res* (Hoboken) 2012; **64**: 465-474 [PMID: 22563589]
61 **McArthur BA**, Dy CJ, Fabricant PD, Valle AG. Long term safety, efficacy, and patient acceptability of hyaluronic acid injection in patients with painful osteoarthritis of the knee. *Patient Prefer Adherence* 2012; **6**: 905-910 [PMID: 23271899 DOI: 10.2147/PPA.S27783]
62 **Goldberg VM**, Buckwalter JA. Hyaluronans in the treatment of osteoarthritis of the knee: evidence for disease-modifying activity. *Osteoarthritis Cartilage* 2005; **13**: 216-224 [PMID: 15727888]
63 **Wang CT**, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. *J Bone Joint Surg Am* 2004; **86-A**: 538-545 [PMID: 14996880]
64 **Kotevoglu N**, Iyibozkurt PC, Hiz O, Toktas H, Kuran B. A prospective randomised controlled clinical trial comparing

the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. *Rheumatol Int* 2006; **26**: 325-330 [PMID: 15959784]
65 **Wobig M**, Bach G, Beks P, Dickhut A, Runzheimer J, Schwieger G, Vetter G, Balazs E. The role of elastoviscosity in the efficacy of viscosupplementation for osteoarthritis of the knee: a comparison of hylan G-F 20 and a lower-molecular-weight hyaluronan. *Clin Ther* 1999; **21**: 1549-1562 [PMID: 10509850]
66 **Divine JG**, Shaffer MD. Use of viscosupplementation for knee osteoarthritis: an update. *Curr Sports Med Rep* 2011; **10**: 279-284 [PMID: 23531974 DOI: 10.1249/JSR.0b013e31822ed1b4]
67 **Maneiro E**, de Andres MC, Fernández-Sueiro JL, Galdo F, Blanco FJ. The biological action of hyaluronan on human osteoartritic articular chondrocytes: the importance of molecular weight. *Clin Exp Rheumatol* 2004; **22**: 307-312 [PMID: 15144124]
68 **Brockmeier SF**, Shaffer BS. Viscosupplementation therapy for osteoarthritis. *Sports Med Arthrosc* 2006; **14**: 155-162 [PMID: 17135962]
69 **Goa KL**, Benfield P. Hyaluronic acid. A review of its pharmacology and use as a surgical aid in ophthalmology, and its therapeutic potential in joint disease and wound healing. *Drugs* 1994; **47**: 536-566 [PMID: 7514978]
70 **Axe JM**, Snyder-Mackler L, Axe MJ. The role of viscosupplementation. *Sports Med Arthrosc* 2013; **21**: 18-22 [PMID: 23314264 DOI: 10.1097/JSA.0b013e3182673241]
71 **Balazs EA**, Denlinger JL. Viscosupplementation: a new concept in the treatment of osteoarthritis. *J Rheumatol Suppl* 1993; **39**: 3-9 [PMID: 8410881]
72 **Greenwald RA**. Oxygen radicals, inflammation, and arthritis: pathophysiological considerations and implications for treatment. *Semin Arthritis Rheum* 1991; **20**: 219-240 [PMID: 2042055]
73 **Watterson JR**, Esdaile JM. Viscosupplementation: therapeutic mechanisms and clinical potential in osteoarthritis of the knee. *J Am Acad Orthop Surg* 2000; **8**: 277-284 [PMID: 11029555]
74 **Moreland LW**. Intra-articular hyaluronan (hyaluronic acid) and hylans for the treatment of osteoarthritis: mechanisms of action. *Arthritis Res Ther* 2003; **5**: 54-67 [PMID: 12718745]
75 **Listrat V**, Ayral X, Patarnello F, Bonvarlet JP, Simonnet J, Amor B, Dougados M. Arthroscopic evaluation of potential structure modifying activity of hyaluronan (Hyalgan) in osteoarthritis of the knee. *Osteoarthritis Cartilage* 1997; **5**: 153-160 [PMID: 9219678]
76 **Bagga H**, Burkhardt D, Sambrook P, March L. Longterm effects of intraarticular hyaluronan on synovial fluid in osteoarthritis of the knee. *J Rheumatol* 2006; **33**: 946-950 [PMID: 16652425]
77 **Wang Y**, Hall S, Hanna F, Wluka AE, Grant G, Marks P, Feletar M, Cicuttini FM. Effects of Hylan G-F 20 supplementation on cartilage preservation detected by magnetic resonance imaging in osteoarthritis of the knee: a two-year single-blind clinical trial. *BMC Musculoskelet Disord* 2011; **12**: 195 [PMID: 21861935 DOI: 10.1186/1471-2474-12-195]
78 **Guidolin DD**, Ronchetti IP, Lini E, Guerra D, Frizziero L. Morphological analysis of articular cartilage biopsies from a randomized, clinical study comparing the effects of 500-730 kDa sodium hyaluronate (Hyalgan) and methylprednisolone acetate on primary osteoarthritis of the knee. *Osteoarthritis Cartilage* 2001; **9**: 371-381 [PMID: 11399102]
79 **Pasquali Ronchetti I**, Guerra D, Taparelli F, Boraldi F, Bergamini G, Mori G, Zizzi F, Frizziero L. Morphological analysis of knee synovial membrane biopsies from a randomized controlled clinical study comparing the effects of sodium hyaluronate (Hyalgan) and methylprednisolone acetate (Depomedrol) in osteoarthritis. *Rheumatology* (Oxford) 2001; **40**: 158-169 [PMID: 11257152]
80 **Amiel D**, Toyoguchi T, Kobayashi K, Bowden K, Amiel ME, Healey RM. Long-term effect of sodium hyaluronate (Hyalgan) on osteoarthritis progression in a rabbit model. *Osteoarthritis Cartilage* 2003; **11**: 636-643 [PMID: 12954234]
81 **Wenz W**, Breusch SJ, Graf J, Stratmann U. Ultrastructural findings after intraarticular application of hyaluronan in a canine model of arthropathy. *J Orthop Res* 2000; **18**: 604-612 [PMID: 11052497]
82 **Pozo MA**, Balazs EA, Belmonte C. Reduction of sensory responses to passive movements of inflamed knee joints by hylan, a hyaluronan derivative. *Exp Brain Res* 1997; **116**: 3-9 [PMID: 9305809]
83 **Ghosh P**. The role of hyaluronic acid (hyaluronan) in health and disease: interactions with cells, cartilage and components of synovial fluid. *Clin Exp Rheumatol* 1994; **12**: 75-82 [PMID: 8162648]
84 **Chhetri DK**, Mendelsohn AH. Hyaluronic acid for the treatment of vocal fold scars. *Curr Opin Otolaryngol Head Neck Surg* 2010; **18**: 498-502 [PMID: 20856119 DOI: 10.1097/MOO.0b013e32833f85d1]
85 **Thirumalai B**, Blamires TL, Brooker L, Deeks J. Heavier molecular weight ocular viscoelastic devices and timing of post-operative review following cataract surgery. *BMC Ophthalmol* 2007; **7**: 2 [PMID: 17291337]
86 **Schnüriger B**, Barmparas G, Branco BC, Lustenberger T, Inaba K, Demetriades D. Prevention of postoperative peritoneal adhesions: a review of the literature. *Am J Surg* 2011; **201**: 111-121 [PMID: 20817145 DOI: 10.1016/j.amjsurg.2010.02.008]
87 **Deans R**, Abbott J. Review of intrauterine adhesions. *J Minim Invasive Gynecol* 2010; **17**: 555-569 [PMID: 20656564 DOI: 10.1016/j.jmig.2010.04.016]
88 **Gomis A**, Miralles A, Schmidt RF, Belmonte C. Intraarticular injections of hyaluronan solutions of different elastoviscosity reduce nociceptive nerve activity in a model of osteoarthritic knee joint of the guinea pig. *Osteoarthritis Cartilage* 2009; **17**: 798-804 [PMID: 19103502 DOI: 10.1016/j.joca.2008.11.013]
89 **Peyron JG**. Intraarticular hyaluronan injections in the treatment of osteoarthritis: state-of-the-art review. *J Rheumatol Suppl* 1993; **39**: 10-15 [PMID: 8410878]
90 **Bannuru RR**, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. *Osteoarthritis Cartilage* 2011; **19**: 611-619 [PMID: 21443958 DOI: 10.1016/j.joca.2010.09.014]
91 **Bellamy N**, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *Cochrane Database Syst Rev* 2006; **(2)**: CD005321 [PMID: 16625635]
92 **Lo GH**, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. *JAMA* 2003; **290**: 3115-3121 [PMID: 14679274]
93 **Modawal A**, Ferrer M, Choi HK, Castle JA. Hyaluronic acid injections relieve knee pain. *J Fam Pract* 2005; **54**: 758-767 [PMID: 16144589]
94 **Arrich J**, Piribauer F, Mad P, Schmid D, Klaushofer K, Müllner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. *CMAJ* 2005; **172**: 1039-1043 [PMID: 15824412]
95 **Medina JM**, Thomas A, Denegar CR. Knee osteoarthritis: should your patient opt for hyaluronic acid injection? *J Fam Pract* 2006; **55**: 669-675 [PMID: 16882439]
96 **Rutjes AW**, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157**: 180-191 [PMID: 22868835 DOI: 10.7326/0003-4819-157-3-201208070-00473]
97 **Printz JO**, Lee JJ, Knesek M, Urquhart AG. Conflict of interest in the assessment of hyaluronic acid injections for osteoarthritis of the knee: an updated systematic review.

J Arthroplasty 2013; **28**: 30-33.e1 [PMID: 23890521 DOI: 10.1016/j.arth.2013.05.034]
98 **Becker LC**, Bergfeld WF, Belsito DV, Klaassen CD, Marks JG, Shank RC, Slaga TJ, Snyder PW, Andersen FA. Final report of the safety assessment of hyaluronic acid, potassium hyaluronate, and sodium hyaluronate. *Int J Toxicol* 2009; **28**: 5-67 [PMID: 19636067 DOI: 10.1177/1091581809337738]
99 **Adams ME**, Lussier AJ, Peyron JG. A risk-benefit assessment of injections of hyaluronan and its derivatives in the treatment of osteoarthritis of the knee. *Drug Saf* 2000; **23**: 115-130 [PMID: 10945374]
100 **Chen AL**, Desai P, Adler EM, Di Cesare PE. Granulomatous inflammation after Hylan G-F 20 viscosupplementation of the knee : a report of six cases. *J Bone Joint Surg Am* 2002; **84-A**: 1142-1147 [PMID: 12107313]
101 **Hall MP**, Band PA, Meislin RJ, Jazrawi LM, Cardone DA. Platelet-rich plasma: current concepts and application in sports medicine. *J Am Acad Orthop Surg* 2009; **17**: 602-608 [PMID: 19794217]
102 **Dohan Ehrenfest DM**, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol* 2009; **27**: 158-167 [PMID: 19187989 DOI: 10.1016/j.tibtech.2008.11.009]
103 **Andia I**, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. *Nat Rev Rheumatol* 2013; **9**: 721-730 [PMID: 24080861 DOI: 10.1038/nrrheum.2013.141]
104 **Anitua E**, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost* 2004; **91**: 4-15 [PMID: 14691563]
105 **Pietrzak WS**, Eppley BL. Platelet rich plasma: biology and new technology. *J Craniofac Surg* 2005; **16**: 1043-1054 [PMID: 16327552]
106 **Woodall J**, Tucci M, Mishra A, Benghuzzi H. Cellular effects of platelet rich plasma: a study on HL-60 macrophage-like cells. *Biomed Sci Instrum* 2007; **43**: 266-271 [PMID: 17487092]
107 **Drengk A**, Zapf A, Stürmer EK, Stürmer KM, Frosch KH. Influence of platelet-rich plasma on chondrogenic differentiation and proliferation of chondrocytes and mesenchymal stem cells. *Cells Tissues Organs* 2009; **189**: 317-326 [PMID: 18689989 DOI: 10.1159/000151290]
108 **Wu W**, Chen F, Liu Y, Ma Q, Mao T. Autologous injectable tissue-engineered cartilage by using platelet-rich plasma: experimental study in a rabbit model. *J Oral Maxillofac Surg* 2007; **65**: 1951-1957 [PMID: 17884521]
109 **Mifune Y**, Matsumoto T, Takayama K, Ota S, Li H, Meszaros LB, Usas A, Nagamune K, Gharaibeh B, Fu FH, Huard J. The effect of platelet-rich plasma on the regenerative therapy of muscle derived stem cells for articular cartilage repair. *Osteoarthritis Cartilage* 2013; **21**: 175-185 [PMID: 23041435 DOI: 10.1016/j.joca.2012.09.018]
110 **Guner S**, Buyukbebeci O. Analyzing the effects of platelet gel on knee osteoarthritis in the rat model. *Clin Appl Thromb Hemost* 2013; **19**: 494-498 [PMID: 22790657 DOI: 10.1177/1076029612452117]
111 **Sun Y**, Feng Y, Zhang CQ, Chen SB, Cheng XG. The regenerative effect of platelet-rich plasma on healing in large osteochondral defects. *Int Orthop* 2010; **34**: 589-597 [PMID: 19434411 DOI: 10.1007/s00264-009-0793-2]
112 **Kwon DR**, Park GY, Lee SU. The effects of intra-articular platelet-rich plasma injection according to the severity of collagenase-induced knee osteoarthritis in a rabbit model. *Ann Rehabil Med* 2012; **36**: 458-465 [PMID: 22977770 DOI: 10.5535/arm.2012.36.4.458]
113 **Saito M**, Takahashi KA, Arai Y, Inoue A, Sakao K, Tonomura H, Honjo K, Nakagawa S, Inoue H, Tabata Y, Kubo T. Intraarticular administration of platelet-rich plasma with biodegradable gelatin hydrogel microspheres prevents osteoarthritis progression in the rabbit knee. *Clin Exp Rheumatol* 2009; **27**: 201-207 [PMID: 19473558]
114 **Qi YY**, Chen X, Jiang YZ, Cai HX, Wang LL, Song XH, Zou XH, Ouyang HW. Local delivery of autologous platelet in collagen matrix simulated in situ articular cartilage repair. *Cell Transplant* 2009; **18**: 1161-1169 [PMID: 19660173 DOI: 10.3727/096368909X12483162197169]
115 **Zhu Y**, Yuan M, Meng HY, Wang AY, Guo QY, Wang Y, Peng J. Basic science and clinical application of platelet-rich plasma for cartilage defects and osteoarthritis: a review. *Osteoarthritis Cartilage* 2013; **21**: 1627-1637 [PMID: 23933379 DOI: 10.1016/j.joca.2013.07.017]
116 **Andia I**, Sánchez M, Maffulli N. Joint pathology and platelet-rich plasma therapies. *Expert Opin Biol Ther* 2012; **12**: 7-22 [PMID: 22171664 DOI: 10.1517/14712598.2012.632765]
117 **Sánchez M**, Azofra J, Anitua E, Andía I, Padilla S, Santisteban J, Mujika I. Plasma rich in growth factors to treat an articular cartilage avulsion: a case report. *Med Sci Sports Exerc* 2003; **35**: 1648-1652 [PMID: 14523300]
118 **Sánchez M**, Anitua E, Azofra J, Aguirre JJ, Andia I. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. *Clin Exp Rheumatol* 2008; **26**: 910-913 [PMID: 19032827]
119 **Sampson S**, Reed M, Silvers H, Meng M, Mandelbaum B. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. *Am J Phys Med Rehabil* 2010; **89**: 961-969 [PMID: 21403592 DOI: 10.1097/PHM.0b013e3181fc7edf]
120 **Kon E**, Buda R, Filardo G, Di Martino A, Timoncini A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc* 2010; **18**: 472-479 [PMID: 19838676 DOI: 10.1007/s00167-009-0940-8]
121 **Filardo G**, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc* 2011; **19**: 528-535 [PMID: 20740273 DOI: 10.1007/s00167-010-1238-6]
122 **Kon E**, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy* 2011; **27**: 1490-1501 [PMID: 21831567 DOI: 10.1016/j.arthro.2011.05.011]
123 **Filardo G**, Kon E, Pereira Ruiz MT, Vaccaro F, Guitaldi R, Di Martino A, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma intra-articular injections for cartilage degeneration and osteoarthritis: single- versus double-spinning approach. *Knee Surg Sports Traumatol Arthrosc* 2012; **20**: 2082-2091 [PMID: 22203046]
124 **Halpern B**, Chaudhury S, Rodeo SA, Hayter C, Bogner E, Potter HG, Nguyen J. Clinical and MRI outcomes after platelet-rich plasma treatment for knee osteoarthritis. *Clin J Sport Med* 2013; **23**: 238-239 [PMID: 23238250 DOI: 10.1097/JSM.0b013e31827c3846]
125 **Sánchez M**, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, Garcia Gutierrez A, Albillos J, Gárate R, Aguirre JJ, Padilla S, Orive G, Anitua E. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy* 2012; **28**: 1070-1078 [PMID: 22840987 DOI: 10.1016/j.arthro.2012.05.011]
126 **Cerza F**, Carnì S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, De Biasi G, Ciuffreda M. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *Am J Sports Med* 2012; **40**: 2822-2827 [PMID: 23104611 DOI: 10.1177/03635465

12461902]
127 **Patel S**, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. *Am J Sports Med* 2013; **41**: 356-364 [PMID: 23299850 DOI: 10.1177/0363546512471299]
128 **Wang-Saegusa A**, Cugat R, Ares O, Seijas R, Cuscó X, Garcia-Balletbó M. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. *Arch Orthop Trauma Surg* 2011; **131**: 311-317 [PMID: 20714903 DOI: 10.1007/s00402-010-1167-3]
129 **Spaková T**, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *Am J Phys Med Rehabil* 2012; **91**: 411-417 [PMID: 22513879 DOI: 10.1097/PHM.0b013e3182aab72]
130 **Filardo G**, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. *BMC Musculoskelet Disord* 2012; **13**: 229 [PMID: 23176112 DOI: 10.1186/1471-2474-13-229]
131 **Say F**, Gürler D, Yener K, Bülbül M, Malkoc M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta Chir Orthop Traumatol Cech* 2013; **80**: 278-283 [PMID: 24119476]

P- Reviewers: Alfredo PP, van den Bekerom MPJ
S- Editor: Wen LL **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com