Update on biological therapies for knee injuries: osteoarthritis

Guilherme Figueiredo Pintaan ·
Adilson Sanches de Oliveira Jr. · Mario Lenza ·
Eliane Antonioli · Mario Ferretti

Published online: 2 July 2014
© Springer Science+Business Media New York 2014

Abstract Osteoarthritis (OA) is a progressive disease that causes functional impairment of the joints. Chronic forms of knee OA have been increasing worldwide, limiting patients' quality of life. Recent studies have sought to increase effectiveness and quality in the development of new therapies, such as platelet-rich plasma, hyaluronic acid, stem cells, and nuclear factor κ B, aimed principally at reducing proinflammatory activity, pain, and degeneration of the knee joints. The goal of this review is to present an update on biological therapies for knee OA and to provide guidance for future OA studies.

Keywords Biological therapies · Knee injuries · Osteoarthritis · Knee osteoarthritis · Hyaluronic acid · Platelet-rich plasma · Mesenchymal stem cells · Tanezumab · Nuclear factor κ B · Calcitonin · Strontium ranelate · Viscosupplementation

Introduction

Osteoarthritis (OA) is a progressive disease resulting in functional impairment. Many people over the age of 65 years demonstrate clinical and radiographic evidence of OA, making this illness the most common disorder of the musculoskeletal system, affecting both small and large joints. In 2005, approximately 27 million Americans were affected by OA [1]. The overall prevalence of OA in symptomatic elderly patients is around 12.1 % [1]. Risk factors for OA include advancing age, obesity, being a postmenopausal woman, previous trauma, malalignment, and genetic factors [2, 3]. As aging,

obesity, and sports-related trauma are increasing and the pathoetiology of OA is multifactorial, the result from a combination of the above factors might contribute to the high prevalence of OA [4, 5••].

Although the prevalence is alarming, the real burden of OA has been underestimated. It is well recognized that the world population is becoming progressively older and the incidence and prevalence are increasing, a fact that contributes to a global problem. [6]. Despite the high prevalence of OA, however, there are no specific guidelines approved by the US Food and Drug Administration for slowing structural joint deterioration. Therefore, OA is treated by a combination of interventions, including lifestyle modification, exercise, and pharmacologic and biomechanical treatments.

OA is a pathology accompanied by an increased presence of inflammatory cytokines and proteolytic molecules in the tissue, which in turn leads to extracellular matrix degeneration and functional impairment. Chondrocytes and synovial cells change their quiescent phenotype in response to an abnormal microenvironment from trauma-induced inflammation [7].

The main proinflammatory cytokines involved in the pathophysiology of OA are interleukin (IL)-1 β , tumor necrosis factor, and IL-6. These cytokines contribute to OA pathogenesis through several mechanisms contributing to the phenotype shift of chondrocytes, through which activated cells increase the expression of catabolic and proinflammatory genes. In addition, these cytokines intensify and maintain OA disease by inducing the production of other proinflammatory cytokines, such as IL-8, IL-15, IL-17, IL-8, IL-21, and leukemia inhibitory factor [8, 9].

The inflammatory microenvironment supports the rise of proteolytic enzymes, matrix metalloproteinases (MMP-13 and MMP-1), and A disintegrin and metalloproteinase with thrombospondin-1 domains 4 and 5. During cartilage degradation, fragments of matrix components are released, such as aggrecan, collagen, and fibromodulin fragments, which

G. F. Pintaan · A. S. de Oliveira Jr. · M. Lenza · E. Antonioli · M. Ferretti (✉)

Division of Orthopaedic Surgery, Hospital Israelita Albert Einstein, Avenida Albert Einstein, 627/701 - 3 Andar/Bloco A1, Morumbi, 05651-901 São Paulo, SP, Brazil
e-mail: ferretti@einstein.br

maintain inflammatory cytokine production [7]. Furthermore, oxide synthase 2, cyclooxygenase (COX)-2, and prostaglandin E gene expression are increased as well, contributing to articular inflammation and destruction by enhancing the activation and production of MMPs and the inhibition of type II collagen proteoglycan synthesis [10].

The treatment of OA has evolved in the past few decades, during which advances in conservative and surgical interventions have been achieved. Conservative treatment has led to better clinical outcomes when combined with modalities such as core treatment, biomechanical interventions, medications, intra-articular injections, and others [11•]. OA management has focused on relieving pain and improving functional symptoms. Consequently, nonsteroidal anti-inflammatory drugs (NSAIDs), pain medications, steroid injections, and viscosupplements have become the most common pharmacologic treatment options. However, the current literature assesses new therapies that might change the way OA is treated, including therapies addressing the pathophysiology described earlier. This article aims to review the biological update on treating knee OA.

Hyaluronic acid

Hyaluronic acid (HA) is a standard constituent of normal synovial fluid and an essential component of joint homeostasis providing lubrication and shock absorption to the knee joint [12•, 13]. In knee OA, both the concentration and the molecular weight of intra-articular HA are reduced (concentration is decreased around 50 %), which decreases the viscoelasticity of synovial fluid. Thus, the goal of intra-articular HA injection is to restore the viscoelasticity of synovial fluid, and it is a common practice despite controversy in the literature [14]. Different types of HAs exist; usually, they differ in molecular weight, dosage, biological features, and preparation methods. The rationale for using HA is an attempt to balance its rheological properties of joint homeostasis, improving biomechanical, environmental, and anti-inflammatory effects [12•, 13, 15].

HA is a glycosaminoglycan and a polysaccharide synthesized by bioactivity of hyaluronan synthase, which has 3 isoforms in humans (HAS1, HAS2, and HAS3). Although HA has been used for a long time, there is no clear evidence of superiority of one type of HA over another [13, 15]. Recent studies have shown not only anti-inflammatory activity but also chondroprotective effects, proposing a potential role for HA in attenuating joint damage [16].

Bannuru et al [17] compared the outcomes of intra-articular HA with those of corticosteroid therapy in patients with knee OA. The authors observed that the corticosteroid injections were significantly more effective than HA up to 4 weeks; however, after 8 weeks, HA was more effective. Bannuru

et al [18] concluded that HA at 8 weeks may have good outcomes when combined with other therapies but with a residual effect until 24 weeks. In addition, HA is superior to acetaminophen, NSAIDs, and COX-2 inhibitors when administered at 8 weeks [18].

Rutjes et al [14] studied the risks and benefits of HA supplementation. Their findings showed small clinical benefits and a high risk of adverse events (AEs). Colen et al [15] commented that the effectiveness of viscosupplementation with HA presents contrasting outcomes in different clinical studies, with no capacity to determine, from clinical studies, the efficacy of HA. Well-designed randomized controlled trials assessing the effects (benefits and harms) of HA for treating knee OA are warranted.

A guideline for OA treatment suggests that HA may be used to decrease pain for a short follow-up in mild or moderate OA [11•].

Platelet-rich plasma

Platelet-rich plasma (PRP) is a product derived from autologous blood with a high platelet concentration in a small volume of plasma. Both plasma and platelets contain growth factors that act during the initial phase of healing and tissue regeneration.

Several growth factors in platelet are present, such as insulin growth factor 1, platelet-derived growth factor, epidermal growth factor (EGF), vascular EGF, transforming growth factor- β , and others. Activities include cellular proliferation, anti-apoptotic activity, cartilage regeneration, collagen synthesis, angiogenesis, and an increase in vascular permeability [19, 20]. Unfortunately, not all the growth factors present in PRP solutions and the concentrations between each individual vary. In addition, the mechanism of action is not totally clear; therefore, it is difficult to determine the effects of each specific growth factor in knee OA.

Patel et al [21], in a level 1 evidence study comparing PRP and saline solution, assessed 78 patients with bilateral knee OA graded 1 or 2 according to the Ahlback classification [22]. They reported a statistically significant difference in favor of PRP with regard to pain, stiffness, and knee function; however, these outcomes were decreased after 6 months. Patients with OA classified as grade 1 responded better than those with grade 2. Mild complications, such as nausea and dizziness, were observed after PRP injection.

Cerza et al [20], in a level 1 evidence study comparing HA with PRP, found that PRP had a significant effect in a short-term follow-up and a continuously improving, sustained effect up to 24 weeks. They also reported that PRP seems more effective than HA in moderate knee OA and Kellgren and Lawrence grade 3 OA.

Sánchez et al [12•], in a multicenter level 1 evidence study, showed a 50 % reduction in the primary outcome of knee pain from baseline to 24 weeks. There was a significantly greater response to PRP than HA with respect to these data. There were no differences in other outcomes between groups; therefore, the authors concluded that PRP demonstrated better results in reducing pain in patients with mild and moderate OA of the knee.

Li et al [23] compared HA with PRP in a level 1 study. There was no difference between PRP and HA groups at 3 months. However, patients treated by PRP showed better functional outcomes after 6 months.

In a randomized controlled trial, Filardo et al [5••] showed that there were no differences between the groups. Despite a significant clinical improvement in up to 1 year follow-up with PRP injections, this treatment was successful only in patients with mild knee joint degeneration. Contrary to what is shown in the current literature for middle-aged patients with mild signs of OA, PRP must not be considered as first-line treatment.

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) are multipotent cells with great replication power found in mature bone marrow. A multi-lineage differentiation potential exists in mesenchymal tissues such as bone, cartilage, adipose tissues, tendons, ligaments, and other tissues. Their apparent capacity to grow in culture, their immunosuppressive activity, and their limited immunogenicity might result in great benefits to clinical practice [13, 24–26]. MSCs delivered as intra-articular injections for knee OA might help improve tissue health by acting as repair cells or decreasing inflammation.

Currently, MSCs have been isolated from human sources such as adipose tissue, synovial membrane, umbilical cord blood, synovial fluid, trabecular bone, infrapatellar fat pad, and periosteum, which have similar characteristics; however, these tissues could vary in their potential for proliferation and differentiation. Their potential to produce therapeutic effects lies in their capacity to regenerate articular cartilage injuries and relieve symptoms and in their immunomodulatory and anti-inflammatory activity, particularly with regard to the secretion of various factors and to direct cell–cell interaction [13, 24, 27].

Researchers reported a functional difference in MSCs isolated from patients with OA compared with those from people without OA. The chondrogenic and adipogenic capacities of MSCs obtained from people with OA apparently are reduced. One theory to explain these differences is that exposure to elevated levels of proinflammatory cytokines and anti-inflammatory drugs might alter the activity status of MSCs. Many studies also have described an age-dependent decrease in the number of progenitor cells isolated from human bone

marrow in elderly patients [28–30]. Currently, however, the literature and clinical practice demonstrate that adequate numbers of MSCs with satisfactory potential for chondrogenic differentiation may be obtained from elderly patients. Therefore, it is suggested that interventions using MSCs to regenerate cartilage in elderly people with OA are feasible [28–30].

In a recent literature search for level 1 evidence, we found the following studies supporting MSC therapy for patients with knee OA. Using scaffold-free MSCs obtained from bone marrow in an experimental animal model of OA by direct intra-articular injection, Singh et al [26] observed a lower degree of cartilage degeneration, osteophyte formation, and subchondral sclerosis compared with the control group 20 weeks after surgery. They concluded that the results with bone marrow-derived MSCs for OA treatment may be promising and that neither the scaffolds nor the culture of trunk cells are essentially necessary for a favorable end point.

Koh et al [25] presented functional results and second-look arthroscopic findings from the intra-articular injection of stem cells (derived from adipose tissue) with arthroscopic lavage for treating knee OA in elderly patients (>65 years). They observed a significant improvement in all clinical outcomes in a 2-year follow-up. Moreover, cartilage status was maintained or improved on second-look arthroscopy in 87.5 % of the elderly patients, and none of the patients required total knee arthroplasty during the same 2-year follow-up period. The authors concluded that this kind of therapy may be an effective option for healing cartilage, reducing pain, and improving function in elderly patients with knee OA.

However, Orth et al [27] discussed new prospects for using stem cells to repair knee cartilage. Their article's conclusion addressed a promising approach using stem cells to repair not only knee cartilage, but also focal defects and generalized OA. Nevertheless, high-quality evidence from randomized controlled trials is needed to standardize current practice, with the main consideration being the patient's welfare.

Systemic delivery of stem cells also has been studied [31]. A systemic infusion of adipose MSCs showed a reduction in OA incidence and severity in an animal model (mice). The success of the therapeutic effect was achieved by reducing the expansion of antigen-specific cellular Th1/Th17, decreasing the production of several inflammatory cytokines and chemokines, inducing the production of IL-10 from local lymph nodes, and stimulating the production of CD4⁺ T lymphocytes and other cell responses [31]. The concept of systemic use of stem cells is interesting because it addresses all peri-articular tissues, including subchondral bone and muscles.

Tanezumab

Nerve growth factor (NGF) is a neurotrophin that plays a key role in neuronal survival by regulating the structure and

function of responsive sensory neurons. During the neonatal period, NGF supports development of the sensory neurons; in adults, NGF is essential in raising awareness of the nociceptor function of neurons with the onset of pain and hyperalgesia in chronic pain. This function may be observed after injury and inflammation, when NGF expression ultimately increases, including in patients with OA, who also express high levels of NGF in their joints [32–35].

Tanezumab is a humanized IgG2 monoclonal antibody that targets NGF with high affinity and specificity, this drug blocks neurotrophic tropomyosin-related kinase A and p75.25 (receptors of NGF). Currently, there are no approved biological therapies for patients with OA. Recent studies showed significant improvement in pain and function of knee OA with tanezumab; however, it should be mentioned that mild to moderate AEs occurred [32–35].

Lane et al [32], in their proof-of-concept study, randomly assigned 450 patients with knee OA to receive 10, 25, 50, 100, or 200 µg/kg body weight of tanezumab or placebo on days 1 and 56. The study evaluated the end points of pain, stiffness, and physical function by using the Western Ontario and McMaster Universities Arthritis Index (WOMAC). Knee pain while walking and overall evaluation of patient response to therapy were the first steps in assessing the effectiveness of the drug. Compared with placebo, tanezumab eventually resulted in a reduction in joint pain and improvement in knee function; however, mild to moderate AEs, such as headache, upper respiratory tract infection, and paresthesia, occurred during testing.

A multicenter phase II study using an open-label, multiple-dose extension of an earlier randomized clinical trial by Schnitzer et al [35] prioritized safety as the end point. Repeat injections of tanezumab in this study showed little evidence of AEs. General knee pain and subject global assessment (SGA) score improved from the beginning of the study through repeated tanezumab injections in 281 patients with moderate and severe knee OA. In their final conclusions, the study investigators reported continued pain relief and improvement in SGA, with a low incidence of side effects.

Nagashima et al [34] investigated the use of tanezumab in 83 patients with moderate and severe OA; the end points included incidence of AEs and change from baseline to week 8 in pain intensity and WOMAC score. At the eighth week, patients in the tanezumab group reported improvement in index knee pain during walking, pain in the past 24 hours, current index knee pain, stiffness, and knee function compared with the placebo group. All AEs were considered mild to moderate in severity. Overall, the use of tanezumab was considered safe and was well tolerated, with the potential to improve pain in patients with moderate or severe knee OA.

Brown et al [36] conducted the first phase III randomized controlled trial demonstrating that NGF blockade by tanezumab has greater analgesic efficacy than placebo in knee OA. The 690 patients who met the study criteria for pain, physical function subscale, and failure of nonopioid pain medications or invasive interventions received 1 of 3 intravenous doses of tanezumab (2.5, 5, or 10 mg) or placebo. Those who received tanezumab had a significant improvement in symptoms compared with the placebo group, with a 55 % to 60 % incidence of AEs, compared with 48 % in the placebo group. In general, the authors concluded that tanezumab was well-tolerated, and reports of worsening OA and/or joint replacement were distributed equally among treatment groups.

In another phase III randomized controlled trial, Spierings et al [33] investigated the efficacy and safety of tanezumab for hip and knee OA. A total of 660 patients were assigned to receive intravenous tanezumab (5 or 10 mg in 8-week intervals), oral controlled-release oxycodone (10–40 mg every 12 hours), or placebo. As the primary outcome, the authors assessed the change from baseline to 8 weeks in WOMAC score and pain. The patients who received tanezumab obtained significant improvements in WOMAC pain score compared with the placebo and oxycodone groups. AEs were more frequent with oxycodone (63.3 %) than tanezumab (40.7 %–44.7 %) or placebo (35.5 %). For all analyses, oxycodone did not differ from placebo, and the results eventually identified the effectiveness of tanezumab for treating OA pain. New signals of safety for use of this drug show promise in the treatment of moderate and severe knee OA.

Nuclear factor κ B transcription factors

Nuclear Factor κ B proteins consist of a family of structurally-related eukaryotic transcription factors, which are related on cellular growth, immune and inflammatory responses and apoptosis. Biological therapies that can block the action of proinflammatory cytokines triggered by mechanical stress that activates nuclear factor κ B (NF- κ B) has great promise in OA treatment [37••]. Biological inhibitors and the use of highly specific drugs and interfering RNAs might seem to be the best strategy to inhibit these proinflammatory actions. However, activated NF- κ B regulates the expression of many cytokines and chemokines, adhesion molecules, inflammatory mediators, and several matrix-degrading enzymes. Research continues to evaluate targeted NF- κ B inhibitors in animal models of OA, as well as how to target these strategies only to affected joints and cartilage to avoid systemic effects [38].

Calcitonin

Calcitonin, a polypeptide hormone of 32 amino acids, is produced in the thyroid gland, specifically in parafollicular cells. In 2013, Mobasheri [37••] published a review on the future of biological therapies for OA with regard to calcitonin. The author found that despite the use of calcitonin to treat hypercalcemia and osteoporosis, several in vitro and in vivo studies and clinical trials are being conducted to confirm its effects on bone mineral density and strength to determine whether it can help patients with OA. A major criticism is the mode of administration; the most effective route is via nasal spray or subcutaneous or intramuscular injection, which is unpleasant for most patients. The types of studies cited by the author seem to suggest a potential for calcitonin in preventing degenerative joint diseases such as OA; however, this requires further study.

Strontium ranelate

Strontium ranelate currently is used to prevent fractures in men and women with severe osteoporosis. In 2 studies by

Reginster et al [39, 40] comparing strontium ranelate with placebo in patients with OA, strontium ranelate seemed to have positive effects, with less degradation of joint space width in the knee, especially with a dosage of 2 g daily. Despite these positive results, however, studies with longer follow-up are needed to determine the drug's safety with long-term use.

Conclusions

Biological therapies increasingly are being sought as alternatives for treating OA. Based on innovative searches, topics such as stem cells, tanezumab, and NF- κ B are becoming more popular in the literature. Please see Table 1 for a summary of biological therapies for knee OA. Although studies using these therapies show great promise for patients with mild to moderate knee OA, they have taken the focus off other treatments and prevention, which are the foundation for OA treatment. Therefore, further research on biological therapies for knee OA is needed to assess the risks and benefits and especially to understand the mechanism of action as well as long-term outcomes.

Table 1 Summary of biological therapies for knee OA

Drug or intervention	Advantage	Disadvantage	Time use	Experimental or clinical use
Hyaluronic acid (HA)	Anti-inflammatory activities, chondroprotective effect, decrease pain for a short follow-up in mild or moderate knee OA.	Inconsistent conclusions, safety need to be proven	Only 1 injection or 3 injections at intervals of 3 wk, depending on the brand of the product.	Clinical and experimental use
Platelet rich plasma (PRP)	PRP seems to be effective for patients with cartilage damage/ moderate knee OA.	Various methods and techniques for obtaining. poor description of the techniques of obtaining inconsistent conclusions, safety need to be proven.	Three injections in a wk or 3 injections at intervals of 3 wk	Clinical and experimental use
Mesenchymal stem cells (MSCs)	Multiline age differentiation potential. Stem cell delivered systemically showed a reduction in the incidence and severity of osteoarthritis in an animal model (mice). Significant improvement in all clinical outcomes in a 2-y follow-up.	Needs further study in Systemic use and intra-articular injection. Safety need to be proven.	One injection intra- articular after arthroscopic lavage.	Experimental
Tanezumab	Showed a significant improvement in pain and function of the knee OA.	Mild to moderate adverse events. Safety need to be proven	Testing phase	Experimental
NF - kappaB transcription factors	Regulates the expression of many cytokines and chemokines, adhesion molecules, inflammatory mediators, and several matrix degrading enzymes.	Inconsistent conclusions, safety need to be proven	Testing phase	Experimental
Calcitonin	Potential for prevention of degenerative joint diseases such as OA.	Safety need to be proven, needs further studies.	Nasal, subcutaneous injection or intramuscular injection. Oral use is in testing phase.	Clinical and experimental use
Strontium ranelate	Positive effects with less degradation of joint space width of the knee.	Safety has to be proven, needs further studies.	2 g/d.	Experimental for OA.

Compliance with Ethics Guidelines

Conflict of Interest Guilherme Figueiredo Pinta, Adilson Sanches de Oliveira Junior, Mario Lenza, Eliane Antonioli, and Mario Ferretti declare that they have no conflict of interest.

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

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum*. 2008;58:26–35.
2. Neustadt DH. Osteoarthritis. In: Rakel RE, editor. *Conn's current therapy*. Philadelphia: W.B. Saunders; 2003. p. 1075–9.
3. Neogi T, Zhang Y. Epidemiology of osteoarthritis. *Rheum Dis Clin N Am*. 2013;39:1–19.
4. Ratzlaff CR, Liang MH. New developments in osteoarthritis: prevention of injury-related knee osteoarthritis: opportunities for the primary and secondary prevention of knee osteoarthritis. *Arthritis Res Ther*. 2010;12:215.
5. Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, et al. 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. *This work suggests that PRP provides clinical improvement in patients with up to 1 year of follow-up. However, the results also show that PRP is not much better than HA and should not be considered first-line treatment for knee OA.*
6. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis*. 2014; In press.
7. Goldring MB, Otero M. Inflammation in osteoarthritis. *Curr Opin Rheumatol*. 2011;23:471–8.
8. Maldonado M, Nam J. The role of changes in extracellular matrix of cartilage in the presence of inflammation on the pathology of osteoarthritis. *Biomed Res Int*. 2013;2013:284873.
9. 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.
10. Heinegård D, Saxne T. The role of the cartilage matrix in osteoarthritis. *Nat Rev Rheumatol*. 2011;7:50–6.
11. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, et al. OARS guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr Cartil*. 2014;22:363–88. *These are the newest guidelines for knee OA management and serve as a database of questions for doctors and patients.*
12. Sánchez M, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, et al. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) vs hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. *Arthroscopy*. 2012;28:1070–8. *This work shows a good safety profile for PRP compared with HA. Also, PRP was more effective in relieving symptoms of mild to moderate knee OA in the short term.*
13. Kon E, Filardo G, Drobnic M, Madry H, Jelic M, van Dijk N, et al. Non-surgical management of early knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2012;20:436–49.
14. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nuesch E, Reichenbach S. Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157:180–91.
15. Colen S, van den Bekerom MP, Mulier M, Haverkamp D. Hyaluronic acid in the treatment of knee osteoarthritis: a systematic review and meta-analysis with emphasis on the efficacy of different products. *BioDrugs*. 2012;26:257–68.
16. Itano N, Sawai T, Yoshida M, et al. Three isoforms of mammalian hyaluronan synthases have distinct enzymatic properties. *J Biol Chem*. 1999;274:25085–92.
17. Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of hyaluronic acid vs corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum*. 2009;61:1704–11.
18. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE. Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis—meta-analysis. *Osteoarthr Cartil*. 2011;19:611–9.
19. Civinini R, Nistri L, Martini C, Redl B, Ristori G, Innocenti M. Growth factors in the treatment of early osteoarthritis. *Clin Cases Miner Bone Metab*. 2013;10:26–9.
20. Cerza F, Carni S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora 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.
21. 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;41:356–64.
22. Ahlbäck S. Osteoarthritis of the knee. A radiographic investigation. *Acta Radiol Diagn (Stockholm)*. 1968;277(Suppl):7–72.
23. Li M, Zhang C, Ai Z, Yuan T, Feng Y, Jia W. Therapeutic effectiveness of intra-knee-articular injection of platelet-rich plasma on knee articular cartilage degeneration. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2011;25:1192–6.
24. Lodi D, Iannitti T, Palmieri B. Stem cells in clinical practice: applications and warnings. *J Exp Clin Cancer Res*. 2011;30:9.
25. Koh YG, Choi YJ, Kwon SK, Kim YS, Yeo JE. Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2013; In press.
26. Singh A, Goel SC, Gupta KK, Kumar M, Arun GR, Patil H, et al. The role of stem cells in osteoarthritis: an experimental study in rabbits. *Bone Joint Res*. 2014;3:32–7.
27. Orth P, Rey-Rico A, Venkatesan JK, Madry H, Cucchiari M. Current perspectives in stem cell research for knee cartilage repair. *Stem Cells Cloning*. 2014;7:1–17.
28. Murphy JM, Dixon K, Beck S, Fabian D, Feldman A, Barry F. Reduced chondrogenic and adipogenic activity of mesenchymal stem cells from patients with advanced osteoarthritis. *Arthritis Rheum*. 2002;46:704–13.
29. De Bari C, Dell'accio F. Mesenchymal stem cells in rheumatology: a regenerative approach to joint repair. *Clin Sci (Lond)*. 2007;113:339–48.
30. Muschler GF, Nitto H, Boehm CA, Easley KA. Age- and gender-related changes in the cellularity of human bone marrow and the prevalence of osteoblastic progenitors. *J Orthop Res*. 2001;19:117–25.
31. González MA, González-Rey E, Rico L, Büscher D, Delgado M. Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells. *Arthritis Rheum*. 2009;60:1006–19.

32. Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD, et al. Tanezumab for the treatment of pain from osteoarthritis of the knee. *N Engl J Med*. 2010;363:1521–31.
33. Spierings EL, Fidelholtz J, Wolfram G, Smith MD, Brown MT, West CR. A phase III placebo- and oxycodone-controlled study of tanezumab in adults with osteoarthritis pain of the hip or knee. *Pain*. 2013;154:1603–12.
34. Nagashima H, Suzuki M, Araki S, Yamabe T, Muto C, Tanezumab investigators. Preliminary assessment of the safety and efficacy of tanezumab in Japanese patients with moderate to severe osteoarthritis of the knee: a randomized, double-blind, dose-escalation, placebo-controlled study. *Osteoarthr Cartil*. 2011;19:1405–12.
35. Schnitzer TJ, Lane NE, Birbara C, Smith MD, Simpson SL, Brown MT. Long-term open-label study of tanezumab for moderate to severe osteoarthritic knee pain. *Osteoarthr Cartil*. 2011;19:639–46.
36. Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, West CR. Tanezumab reduces osteoarthritic knee pain: results of a randomized, double-blind, placebo-controlled phase III trial. *J Pain*. 2012;13:790–8.
- 37.●● Mobasheri A. The future of osteoarthritis therapeutics: emerging biological therapy. *Curr Rheumatol Rep*. 2013;15:385. *This article presents an overview of the emerging biological therapies for OA, focusing on new concepts of molecular stimulation of neurogenesis and angiogenesis, tanezumab for knee OA pain, and an update on NF-κB.*
38. Marcu KB, Otero M, Olivetto E, Borzi RM, Goldring MB. NF-kappaB signaling: multiple angles to target OA. *Curr Drug Targets*. 2010;11:599–613.
39. Reginster JY, Badurski J, Bellamy N, Bensen W, Chapurlat R, Chevalier X, et al. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomized placebo-controlled trial. *Ann Rheum Dis*. 2013;72:179–86.
40. Reginster JY, Beaudart C, Neuprez A, Bruyère O. Strontium ranelate in the treatment of knee osteoarthritis: new insights and emerging clinical evidence. *Ther Adv Musculoskelet Dis*. 2013;5: 268–76.