47 *Osteoarthritis—An Update*

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Abstract: Osteoarthritis is a major problem in the elderly associated with morbidity. This review is restricted to primary osteoarthritis of knee. It reviews the available modalities of therapy with their efficacy and an account of some new experimental therapies.

The goals of therapy are control of pain and improvement in function and health-related quality of life, and minimize side effects of therapy. The ACR Subcommittee on OA Guidelines has developed recommendations for treatment; however, these are not fixed, rigid mandates, and the Subcommittee recognizes that the final decision concerning the therapeutic regimen for an individual patient rests with the treating physician.

The therapy includes both nonpharmacologic modalities and drugs. Non-pharmacological therapy must be used in conjunction with drugs. Surgical interventions may be required in selected cases. Oral agents include use of acetaminophen, NSAIDs, selective COX-2 inhibitors, opioid analgesics for pain relief. Agent with modulating properties of the course of the osteoarthritic condition, the so-called SYSADOA (Symptomatic Slow Acting Drugs for Osteoarthritis) and structure modifiers include glucosamine sulfate, chondroitin sulfate and diacerein. The SYSADOA have symptomatic effects and can modify the structure. However, there are many conflicting reports about their efficacy. Efficacy of bisphosphonate, MMP inhibitors and PPARs to treat knee OA and prevent its structural progression is under evaluation.

An alternative approach to the use of oral agents in the palliation of joint pain is the use of intra-articular therapy such as hyaluronan (hyaluronic acid) or glucocorticoids which give short-term pain relief. Intra-articular injection of IL-1 receptor antagonist (IL-1Ra) may be associated with significant improvements.

Arthroscopic debridement, arthroscopic lavage and joint replacement are important surgical interventions. There are new other modalities which are being tried, e.g. compartmental knee replacements, autologous chondrocyte transplantation, cartilage repair using mesenchymal stem cells, and autologous osteochondral plugs (mosaicplasty).

Future therapies include aggrecanase inhibition, gene therapy, orthokine and targeting synovial inflammation.

INTRODUCTION

Osteoarthritis is a major problem in the elderly associated with morbidity. This review is restricted to primary osteoarthritis of knee. It reviews the available modalities of therapy with their efficacy and an account of some new experimental therapies.

Osteoarthritis (OA) is currently defined by the American College of Rheumatology (ACR) as a "heterogeneous group of conditions that leads to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins.[1]

Approximately 25 percent of persons 55 years of age or older have had knee pain on most days in a month in the past year,[2,3] and about half of them have radiographic osteoarthritis in the

knee, a group considered to have symptomatic osteoarthritis. Physical disability arising from knee OA can be severe and loss of functional capacity reduces quality of life.[4,5] The disease can exist without radiographic evidence of osteoarthritis of the knee, an imaging procedure insensitive to early disease.

The etiology of OA is multifactorial, with inflammatory, metabolic, and mechanical causes. A number of environmental risk factors, such as obesity, occupation, and trauma, may initiate various pathological pathways.[1] Though OA indicates the degeneration of articular cartilage together with changes in subchondral bone; an intra-articular inflammatory component should not be overlooked as it forms the basis of therapeutic strategies.

Although there is no known cure for OA, treatment is directed to reduce pain, maintain and/or improve joint mobility, and limit functional impairment.[6] In 1995, the American College of Rheumatology (ACR) published recommendations for the medical management of OA of the hip and knee.[7] Several therapeutic strategies have been developed for better medical treatments for OA.[8]

However, development of disease-modifying osteoarthritis drugs (DMOADs) encounters obstacles like regulatory issues, length of clinical trials, the lack of validation and consensus on new biological markers. Moreover, the duration of treatment is likely to be lifelong.

DIAGNOSIS

OA knee is classified on the basis of ACR criteria as given in Table 47.1.[9]

Table 47.1: Criteria for Classification of Idiopathic Osteoarthritis (OA) of the Knee [1986]*

Clinical and laboratory	*Clinical and radiographic*	*Clinical†*
Knee pain	Knee pain	Knee pain
+ at least 5 of 9:	+ at least 1 of 3:	+ at least 3 of 6:
– Age > 50 years	– Age > 50 years	– Age > 50 years
– Stiffness < 30 minutes	– Stiffness < 30 minutes	– Stiffness < 30 minutes
– Crepitus	– Crepitus	– Crepitus
– Bony tenderness	+ Osteophytes	– Bony tenderness
– Bony enlargement	– Bony enlargement	
– No palpable warmth	– No palpable warmth	
– ESR < 40 mm/hour		
– RF <1:40		
– SF OA		
92% sensitive	91% sensitive	95% sensitive
75% specific	86% specific	69% specific

ESR = erythrocyte sedimentation rate (Westergren); RF = rheumatoid factor; SF OA = synovial fluid signs of OA (clear, viscous, or white blood cell count < 2,000/mm^3). † Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific

TREATMENT

The goals of therapy are control of pain and improvement in function and health-related quality of life, and minimize side effects of therapy. The therapy includes both nonpharmacologic modalities and drugs. The ACR Subcommittee on OA Guidelines[6] has developed recommendations for treatment; however these are not fixed, rigid mandates, and the Sub-

committee recognizes that the final decision concerning the therapeutic regimen for an individual patient rests with the treating physician.

Non-pharmacologic Therapy

Disuse atrophy due to unloading of the painful extremity leads to Quadriceps weakness commonly among patients with knee OA.[10] Quadriceps weakness may be a risk factor for the development of knee OA, presumably by decreasing stability of the knee joint.[11] The beneficial effects of both quadriceps strengthening and aerobic exercise for patients with knee OA were confirmed in the Fitness Arthritis and Seniors Trial.[12]

Decrease in proprioception, has also been documented in patients with knee OA.[13,14] Hurley and Scott[15] showed that exercise regimen also improved knee joint position sense along with quadriceps strength. However, if the knee is very painful during an exercise, then that exercise should be avoided.[2]

Appetite suppressant and low-calorie diet is recommended for overweight patients with knee OA.[16]

Pharmacological Therapy

Acetaminophen

Both, the American College of Rheumatology (ACR) and the European League of Associations of Rheumatology (EULAR), recommendations for the use of pharmacological therapy in the treatment of patients with osteoarthritis of knee advocate acetaminophen (paracetamol) as first-line oral therapy for mild to moderate pain because it is more efficacious than placebo and is generally considered to be safe and well-tolerated. Data obtained in recent trials and the results of a meta-analysis, however, show that acetaminophen is not as efficacious as nonsteroidal anti-inflammatory drugs (NSAIDs) for pain at rest and pain on motion.[17] Use of high-dose acetaminophen (> 2 g/day) may be associated with increased risk for serious upper gastrointestinal adverse events as that associated with NSAIDs. Acetaminophen can be given up to doses of 4 g per day.

Paracetamol is effective in the treatment of knee OA and that in many patients it is comparable with ibuprofen in the short-term[18] and equivalent to naproxen.[19]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

For treating the pain of osteoarthritis of the knee, nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase 2 (COX 2) inhibitors are more efficacious than acetaminophen.[4,20-22]

There has been speculation that COX 2 selective agents are more beneficial than conventional NSAIDs, particularly in those at higher risk of adverse gastrointestinal side effects. Low doses of anti-inflammatory medications[23] are less efficacious but better tolerated than high doses.[24] Though the use of COX 2 inhibitors[25] decreases the potential gastric toxicity of conventional NSAIDs, the results of recent trials showed increased cardiovascular risk with these agents limiting their use.[26] Misoprostol or proton-pump inhibitors may be used for GI protection with NSAIDs.

Opioid Analgesics

Opioid analgesics, with or without paracetamol, are useful alternatives in patients in whom NSAIDs, including COX 2 selective inhibitors, are contraindicated or ineffective.[27] However, there may be increased risk of adverse side effects, particularly in the elderly, and potential dependence with use of opioids.

Tramadol, a centrally acting oral analgesic, is a synthetic opioid agonist that also inhibits reuptake of norepinephrine, and serotonin may be used for the treatment of moderate-to-severe pain.[28]

Glucosamine and Chondroitin Sulphate

Agent with modulating properties of the course of the osteoarthritic condition, the so-called SYSADOA (Symptomatic Slow Acting Drugs for Osteoarthritis) and "structure modifiers" have been defined. These include glucosamine sulfate, chondroitin sulfate and diacerein. The SYSADOA have symptomatic effects and can modify the structure.[29] However, their limited advantage over the placebo makes it necessary to evaluate the clinical relevance of their application before recommending their generalized use. There are many conflicting reports about their efficacy. The dietary supplements of glucosamine and chondroitin sulfate have been advocated, especially in the lay media, as safe and effective options for the management of symptoms of osteoarthritis.[30]

Chondroitin sulphate (CS) produces a slow but gradual decrease in the clinical symptoms of OA that could last for a long period of time after treatment. CS could also act as an anti-inflammatory and chondroprotective agent by modifying the structure of cartilage. Use of glucosamine-HCl and CS is safe but requires chronic administration.[31-33]

Glucosamine sulfate is more effective than glucosamine hydrochloride and taking chondroitin sulfate in combination with glucosamine sulfate may have an additive effect.[34]

Recently a multicenter, double-blind, placebo- and celecoxib-controlled Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) evaluated their efficacy and safety as a treatment for knee pain from osteoarthritis.[30] glucosamine and chondroitin sulfate alone or in combination did not reduce pain effectively in the overall group of patients with osteoarthritis of the knee. However, the study suggests that the combination of glucosamine and chondroitin sulfate may be effective in the subgroup of patients with moderate-to-severe knee pain.

In a randomized clinical trial on the long-term effects of glucosamine sulphate on OA progression there was no significant joint space loss in the patients on glucosamine sulphate. Also knee OA symptoms improved after treatment with glucosamine sulphate. This suggested that long-term combined structure-modifying and symptom-modifying effects of glucosamine sulphate could be used as a disease-modifying agent in OA.[35] These findings were also supported by two other studies conducted by Pavelka[36] and Bruyere.[37]

Diacerein

Diacerein is a slow acting symptomatic treatment of osteoarthritis which has demonstrated efficacy on functional manifestations of osteoarthritis and on the structural component. It acts by inhibition of interleukin-1 (IL-1) synthesis, the main cytokine involved in cartilage destruction, and also has activity on the synthesis of proteoglycans, and hyaluronic acid, the principal components of cartilage.[38]

Rhein, the active metabolite of diacerein, inhibits interleukin-1 activity reducing the collagenase production in articular cartilage. Rhein dose-dependently inhibits superoxide anion production, chemotaxis and phagocytic activity of neutrophils, and macrophage migration and phagocytosis.[39]

Diacerein is entirely converted into rhein before reaching the systemic circulation. Rhein itself is either eliminated by the renal route (20%) or conjugated in the liver to rhein glucuronide (60%) and rhein sulfate (20%); these metabolites are mainly eliminated by the kidney. Liver disease does not change the kinetics of diacerein. In mild-to-severe renal insufficiency a 50% reduction of the standard daily dose is recommended. Except for moderate and transient digestive disturbances (soft stools, diarrhea), diacerein is well-tolerated.[40]

The recommended daily dose of diacerein for symptomatic relief of patients with knee OA is 50 mg twice daily.[41]

Diacerein is shown to inhibit indomethacin-induced gastric ulceration in a dose-dependent manner, a beneficial effect in therapy as NSAIDs are important in therapeutics.[42]

Antiresorptive Agents

Recent research has highlighted the importance of subchondral bone as a target for therapeutic intervention and disease modification in OA.[43,44] Joints affected by OA exhibit increased bone turnover, and may benefit from the antiresorptive agents such as bisphosphonates.

Carbone and colleagues showed that women treated with both alendronate and estrogen exhibited significantly less knee subchondral bone attrition and bone marrow edema-like abnormalities. However, there was no significant effect on progression of cartilage damage.[45]

Spector and colleagues examined the effect of risedronate, which revealed a definite trend toward improvement in both joint structure and symptoms in patients with primary knee OA.[46]

However, the use of a bisphosphonate to treat knee OA and prevent its structural progression needs to be explored further.

MMP Inhibitors

It is now appreciated that tetracycline analogues can inhibit MMPs, and multiple underlying mechanisms have been proposed.

In a study, however, doxycycline did not reduce the mean severity of joint pain. After 16 months of treatment, the mean loss of joint space width (JSW) in the index knee in the doxycycline group was 40% less than in the placebo group.[47]

PPARs

Among the PPARs, it appears that PPAR is the key factor involved as an anti-inflammatory agent. It has been found to be expressed in various cells, including human chondrocytes and synovial fibroblasts.[48,49] *In vivo*, the synthetic PPAR ligands rosiglitazone and pioglitazone were capable of improving signs of inflammation and histological lesions in a collagen-induced arthritis model[50] and an OA guinea pig model,[51] respectively. Their role in human beings needs to be evaluated.

Local Applications

The use of topical analgesics (e.g., methylsalicylate or capsaicin cream) is appropriate as either adjunctive treatment or monotherapy.[6,52] Topical capsaicin reversibly desensitizes nociceptive C fibers by acting on the VR-1 vaniloid receptors.[4]

Studies comparing diclofenac gel with ketoprofen gel[53] and piroxicam gel with oral ibuprofen[54] showed equal efficacy between treatments. Topical NSAIDs have a good safety record.

INTRA-ARTICULAR INJECTIONS

Hyaluronan

An alternative approach to the use of oral agents in the palliation of joint pain is the use of intra-articular therapy such as hyaluronan (hyaluronic acid) or glucocorticoids.[6]

Joint lubrication is naturally provided by hyaluronic acid in the synovial fluid. Hyaluronan is present in abundance in normal young and healthy joints. In degenerative OA, hyaluronan is smaller in size and molecular weight, and its concentration is diminished. The decrease in joint

hyaluronan content decreases lubrication and the shock absorbing mechanism in osteoarthritic joint. Viscosupplementation partially may improve these joint properties.[8]

In clinical trials of intra-articular hyaluronan preparations, pain relief was significantly greater than that with placebo, and comparable with oral NSAIDs.[55-57] Pain relief was also comparable with or greater than that with intra-articular glucocorticoids.[57] Jubb and colleagues[58] showed that those with milder radiographic disease at baseline had lesser progression of JSN with hyaluronic acid treatment. Transient mild-to-moderate pain at the injection site may occur with increase in joint pain and swelling following hyaluronan injection.

Two recent meta-analyses[59,60] reported statistically significant but limited efficacy of intra-articular hyaluronan injection.

Several HA preparations exist, in two main categories: high molecular and low molecular weight. It has been postulated that those preparations with a high molecular weight may have a superior effect.[4]

Corticosteroids

The pain and secondary inflammation in moderate to severe OA can be effectively relieved by intra-articular injection of steroids.[8] In a randomized, double-blind, placebo-controlled setting with intra-articular injections of triamcinolone acetonide 40 mg every 3 months for up to 2 years. At the 1-year and 2-year follow-up evaluations, no difference was noted between the two treatment groups with respect to loss of joint space over time.[61] However, the steroid injected knees exhibited a trend toward greater symptom improvement. These findings support the long-term safety of intra-articular steroid injections in patients with symptomatic knee OA without any disease modifying activity.

Intra-articular glucocorticoid injections are of value in the treatment of acute knee pain in patients with signs of local inflammation with a joint effusion.[57-62] Injection can be used as mono-therapy in selected patients or as an adjunct to systemic therapy with an analgesic, a nonselective NSAID, or a COX-2-specific inhibitor. Intra-articular injections of corticosteroid are effective but give relatively short lived benefit.[4]

IL-1Ra

Intra-articular injection of IL-1 receptor antagonist (IL-1Ra) in patients with symptomatic knee OA was recently assessed. Significant improvements on knee OA symptoms were still observed at 3 months in the patients who received 150 mg IL-1Ra.[63] However, another study did not confirm these results.[64]

Surgery

Presently many established and novel surgical approaches are available for OA knee. Compartmental knee replacements are gaining popularity, especially for medial compartment arthritis. Minimally invasive surgery (i.e., quadriceps sparing arthroplasty) has become very popular in the last few years and is being used routinely for unicompartmental knee replacement.[65]

In appropriately selected patients who are not yet candidates for total joint arthroplasty, osteotomy may provide pain relief and prevent progression of disease.[6]

Autologous chondrocyte transplantation,[66] cartilage repair using mesenchymal stem cells,[67] and autologous osteochondral plugs (mosaicplasty)[68] are being investigated for repair of focal chondral defects.

Arthroscopic debridement, arthroscopic lavage are established procedures for OA knee. However, in a recent study, arthroscopic lavage with or without debridement was found to be no better than a placebo procedure in improving knee pain and self-reported function. Indeed, at

some points during follow-up, objective function was significantly worse in the debridement group than in the placebo group.[69]

Joint replacement is an irreversible intervention used in those for whom other treatment modalities have failed and who generally have more severe disease. The effectiveness of total knee replacement (TKR) in knee OA is well established in those severely incapacitated. The indications for an operative procedure are severe daily pain and X-ray evidence of joint space narrowing.[70-71]

FUTURE THERAPIES

Aggrecanase Inhibition

Proteases are responsible for the cleavage of aggrecan. Two such enzymes were found in articular tissues and named aggrecanase-1 and aggrecanase-2.[72,73] These enzymes belong to the ADAMTS family and were further designated ADAMTS-4 and ADAMTS-5, respectively. Recent reports have shown that ADAMTS-5 is the predominant enzyme involved in the OA process.[74,75] A selective inhibitor of aggrecanase and MMP-13 was recently reported.[76] This therapeutic approach may hold some promise for the future.

Gene Therapy

Several candidate genes have been identified as potential targets for the treatment of OA,[77-81] including a wide range of molecules such as cathepsin K, caspases, MMPs and cytokines.

Gene therapy controls the expression of a number of genes that are responsible for the synthesis of factors involved in cartilage degradation and/or those that promote cartilage repair.[82]

Studies have shown beneficial effects of using different *in vivo* gene therapy strategies with IL-1Ra in two OA experimental models.[83-85]

Strategies that are capable of stimulating cartilage anabolism and joint repair include the use of growth factors such as members of the transforming growth factor-β family, insulin-like growth factor IGF-1 and fibroblast growth factor, which were demonstrated to stimulate the formation of hyaline cartilage-like repair tissue. Transfer of these genes into OA joint cells, such as the chondrocytes, may represent an interesting therapeutic DMOAD option to repair cartilage lesions.

Targeting Synovial Inflammation: Interleukin-1β

Inhibition of the production/activity of IL-1β, can be achieved by receptor blockade, neutralization of the cytokine by soluble receptors or monoclonal antibody, blocking the formation of active IL-1β, or inhibiting the IL-1β cellular signalling pathways. Recombinant human IL-1Ra, Anakinra, when injected subcutaneously, is safe and well tolerated in a diverse population of patients with RA.[86] However, its rapid clearance and variable accumulation in the OA joints has promoted the use of delivering IL-1Ra intra-articularly.

IL-1β is primarily synthesized as a precursor (pro-IL-1β), and must be cleaved by a cysteine-dependent protease, named IL-1β converting enzyme (or caspase-1), to generate the mature cytokine. It is also responsible for the cleavage and release of IL-18. Thus, inhibition of this enzyme will block activation of two very potent proinflammatory cytokines. IL-1β converting enzyme inhibitor was found to reduce the progression of joint damage in two experimental mouse models of OA.[87]

IL-1 activity is mediated by its binding only to type I receptor. After IL-1 binding to its type I receptor, there is induction of multiple phosphorylation-dependent signalling pathways which includes the serine-threonine kinases of the mitogen-activated protein kinase family and nuclear

factor-κB cascades. The mitogen-activated protein kinase superfamily is composed of at least three signalling pathways: the extracellular signal-regulated protein kinases, the c-Jun amino-terminal kinases or stress-activated protein kinases, and the p38 family of kinases.

An experimental *in vivo* study has reported a therapeutic effect of a specific extracellular signal-regulated protein kinase inhibitor, namely PD198306, in experimental rabbit OA.[88] Recently it was reported that phenyl N-tert-butylnitrone, a spin-trap agent, downregulates IL-1-induced MMP-13 expression via the inhibition of the c-Jun amino-terminal kinase pathway in OA chondrocytes.[89]

The p38 inhibitor has anti-inflammatory effects in cartilage explants and in animal models.[90]

Orthokine

An alternative therapy, based on the intra-articular injection of autologous conditioned serum, is used in Europe. This product, known as Orthokine, is generated by incubating venous blood with etched glass beads. In this way, peripheral blood leukocytes produce elevated amounts of the interleukin-1 receptor antagonist and other anti-inflammatory mediators that are recovered in the serum. Considerable symptomatic relief has been reported in clinical trials of this product.[91]

REFERENCES

1. Sarzi-Puttini P, Cimmino MA, et al. Osteoarthritis: an overview of the disease and its treatment strategies. Semin Arthritis Rheum 2005; 35(1 Suppl 1):1-10.
2. Felson DT. Osteoarthritis of the knee. N Engl J Med 2006;354:841-9.
3. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001;60:91-7.
4. KM Jordan, N K Arden, M Doherty, et al. EULAR Recommendations 2003: an evidence based osteoarthritis: approach to the management of knee Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003;62;1145-55.
5. Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham study. Am J Publ Health 1994;84:351-8.
6. Altman RD, Hochberg MC, Moskowitz RW, Schnitzer TJ, for American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee. Arthritis Rheum 2000;43:1905-15.
7. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. Arthritis Rheum 1995;38:1541-6.
8. Pelletier J, Martel-Pelletier J, Raynauld J. Most recent developments in strategies to reduce the progression of structural changes in osteoarthritis: today and tomorrow. Arthritis Research & Therapy 2006;8:206.
9. Altman R, Asch E, Bloch D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039-49.
10. Slemenda C, Brandt KD, Heilman DK, et al. Quadriceps weakness and osteoarthritis of the knee. Ann Intern Med 1997;127:97-104.
11. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. Rheum Dis Clin North Am 1999;25:283-98.
12. Ettinger WH Jr, Bums R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis: the Fitness Arthritis and Seniors Trial (FAST). JAMA 1997;277:25-31.
13. Hurley MV, Scott DL, Rees J, Newham DJ. Sensorimotor changes and functional performance in patients with knee osteoarthritis. Ann Rheum Dis 1997;56:641-8.
14. Sharma L, Pai Y-C, Holtkamp K, Rymer WZ. Is knee joint proprioception worse in the arthritic knee versus the unaffected knee in unilateral knee osteoarthritis. Arthritis Rheum 1997;40:1518-25.
15. Hurley MV, Scott DL. Improvements in quadriceps sensorimotor function and disability of patients with knee osteoarthritis following a clinically practicable exercise regime. Br J Rheumatol 1998;37:1181-7.
16. Toda Y, Toda T, Takemura S, Wada T, Morimoto T, Ogawa R. Change in body fat, but not body weight or metabolic correlates of obesity, is related to symptomatic relief of obese patients with knee osteoarthritis after a weight control program. J Rheumatol 1998;25:2181-6.
17. Hochberg MC, Dougados M. Pharmacological therapy of osteoarthritis. Best Pract Res Clin Rheumatol 2001;15: 583-93.
18. Amadio P, Cummings DM. Evaluation of acetaminophen in the management of osteoarthritis of the knee. Cur Ther Res 1983;34:59-66.

19. Williams HJ, Ward JR, Egger MJ, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. Arthritis Rheum 1993;36:1196-206.
20. Felson DT. The verdict favors nonsteroidal antiinflammatory drugs for treatment of osteoarthritis and a plea for more evidence on other treatments. Arthritis Rheum 2001;44:1477-80.
21. Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee. JAMA 2002; 287: 64-71.
22. Bensen WG, Fiechtner JJ, McMillen JI, et al. Treatment of osteoarthritis with celecoxib, a cyclo-oxygenase-2 inhibitor: a randomised controlled trial. Mayo Clin Proc 1999;74: 1095-1105.
23. Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991;114:257-63.
24. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. N Engl J Med 1998;338:719-26.
25. Fries JF, Williams CA, Bloch DA. The relative toxicity of nonsteroidal antiinflammatory drugs. Arthritis Rheum 1991;34:1353-60.
26. Fitzgerald GA. Coxibs and cardiovascular disease. N Engl J Med 2004;351:1709-11.
27. Schnitzer TJ, Kamin M, Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain. Arthritis Rheum 1999;42:1370-7.
28. Dalgin P, and the TPS-OA Study Group. Comparison of tramadol and ibuprofen for the chronic pain of osteoarthritis [abstract]. Arthritis Rheum 1997;40Suppl9:S86.
29. Mulero MJ. Pharmacological treatment of osteoarthritis: Expectations and reality. Rev Clin Esp 2005;205:168-71.
30. Clegg DO, Reda DJ, Harris CL. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. N Engl J Med 2006;354:795-808.
31. Michel BA, Stucki G, Frey D, et al. Chondroitins 4 and 6 sulfate in osteoarthritis of the knee: a randomized, controlled trial. Arthritis Rheum 2005;52:779-86.
32. Uebelhart D, Malaise M, Marcolongo R, et al. Intermittent treatment of knee osteoarthritis with oral chondroitin sulfate: a one-year, randomized, double-blind, multicenter study versus placebo. Osteoarthritis Cartilage 2004;12:269-76.
33. Morreale P, Manopulo R, Galati M, Boccanera L, Saponati G, Bocchi L. Comparison of the antiinflammatory efficacy of chondroitin sulphate and diclofenac sodium in patients with knee osteoarthritis. J Rheumatol 1996;23:1385-91.
34. Hochberg MC. Nutritional Supplements for Knee Osteoarthritis: Still No Resolution N Engl J Med 2006;354:858-60.
35. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebocontrolled clinical trial. Lancet 2001;357:51-56.
36. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162: 2113-23.
37. Bruyere O, Pavelka K, Rovati LC, et al. Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: evidence from two 3-year studies. Menopause 2004;11:138-43.
38. Solignac M. Mechanisms of action of diacerein, the first inhibitor of interleukin-1 in osteoarthritis. Presse Med 2004; 33(9 Pt 2): S10-2.
39. Spencer CM, Wilde MI. Diacerein. Drugs 1997;53:98-106.
40. Nicolas P, Tod M, Padoin C, Petitjean O. Clinical pharmacokinetics of diacerein. Clin Pharmacokinet 1998;35 347-59.
41. Pelletier JP, Yaron M, Haraoui B, et al. Efficacy and safety of diac-erein in osteoarthritis of the knee: a double-blind, placebo-controlled trial. The Diacerein Study Group. Arthritis Rheum 2000;43:2339-48.
42. Tamura T, Yokoyama T, Ohmori K. Effects of diacerein on indomethacin-induced gastric ulceration. Pharmacology 2001;63:228-33.
43. Martel-Pelletier J, Lajeunesse D, Pelletier JP. Etiopathogenesis of osteoarthritis. In: Koopman WJ, editor. Arthritis and Allied Conditions A Textbook of Rheumatology. Baltimore MA, Lippincott, Williams & Wilkins; 2005;2199-26.
44. Lajeunesse D, Massicotte F, Pelletier JP, Martel-Pelletier J. Subchondral bone sclerosis in osteoarthritis: Not just an innocent bystander. Modern Rheumatol 2003;13:7-14.
45. Carbone LD, Nevitt MC, Wildy K, et al. The relationship of antiresorptive drug use to structural findings and symptoms of knee osteoarthritis. Arthritis Rheum 2004;50:3516-25.
46. Spector TD, Conaghan PG, Buckland-Wright JC, et al. Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial. Arthritis Res Ther 2005;7:R625-33.
47. Brandt KD, Mazzuca SA, Katz BP, et al. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum 2005;52:2015-25.
48. Fahmi H, Di Battista JA, Pelletier JP, Mineau F, Ranger P, Martel-Pelletier J. Peroxisome proliferator-activated receptor gamma activators inhibit interleukin-1beta-induced nitric oxide and matrix metalloproteinase 13 production in human chondrocytes. Arthritis Rheum 2001;44:595-607.
49. Fahmi H, Pelletier JP, Di Battista JA, Cheung HS, Fernandes J, Martel-Pelletier J. Peroxisome proliferator-activated receptor gamma acitvators inhibit MMP-1 production in human synovial fibroblasts by reducing the activity of the activator protein 1. Osteoarthritis Cartilage 2002;10:100-108.
50. Cuzzocrea S, Mazzon E, Dugo L, et al. Reduction in the evolution of murine type II collagen-induced arthritis by treatment with rosiglitazone, a ligand of the peroxisome proliferator-activated receptor gamma. Arthritis Rheum 2003;48:3544-56.

51. Kobayashi T, Notoya K, Naito T, et al. Pioglitazone, a peroxisome proliferator-activated receptor gamma agonist, reduces the progression of experimental osteoarthritis in guinea pigs. Arthritis Rheum 2005;52:479-87.
52. Deal CL, Schnitzer TJ, Lipstein E, et al. Treatment of arthritis with topical capsaicin: a double-blind trial. Clin Ther 1991;13:383-95.
53. Waikakul S, Penkitti P, Soparat K, Boonsanong W. Topical analgesics for knee arthrosis: a parallel study of ketoprofen gel and diclofenac gel. J Med Assoc Thai 1997;80:593-7.
54. Dickson DJ. A double blind evaluation of topical piroxicam gel with oral ibuprofen in osteoarthritis of the knee. Curr Ther Res 1991;49:199-207.
55. Altman RD, Moskowitz RW, and the Hyalgan Study Group. Intra-articular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: A randomized clinical trial. J Rheumatol 1998;25:2203-12.
56. Adams ME, Atkinson MH, Lussier AJ, et al. The role of vi scosupplementation with hylan G-F 20 (Synvisc) in the treatment of osteoarthritis of the knee: a Canadian multicenter trial comparing hylan G-F 20 alone, hylan G-F 20 with non-steroidal anti-inflammatory drugs (NSAIDs) and NSAIDs alone. Osteoarthritis Cartilage 1995;3:213-25.
57. Kirwan JR, Rankin E. Intra-articular therapy in osteoarthritis. Baillieres Clin Rheumatol 1997;11: 769-94.
58. Jubb RW, Piva S, Beinat L, Dacre J, Gishen P. A one-year, randomised, placebo (saline) controlled clinical trial of 500-730 kDa sodium hyaluronate (Hyalgan) on the radiological change in osteoarthritis of the knee. Int J Clin Pract 2003;57:467-74.
59. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. JAMA 2003;290: 3115-21.
60. 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 2005;2:CD005321.
61. Raynauld JP, Buckland-Wright C, Ward R, et al. Safety and efficacy of long-term intraarticular steroid injections in osteoarthritis of the knee: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2003;48:370-7.
62. Creamer P. Intra-articular corticosteroid injections in osteoarthritis: do they work and if so, how? Ann Rheum Dis 1997;56:634-6.
63. Chevalier X, Giraudeau B, Conrozier T, Marliere J, Kiefer P, Goupille P. Safety study of intraarticular injection of interleukin 1 receptor antagonist in patients with painful knee osteoarthritis: a multicenter study. J Rheumatol 2005;32:1317-23.
64. Chevalier X, Goupille P, Beaulieu AD, et al. Results from a double blind, placebo-controlled, multicenter trial of a single intra-articular injection of anakinra (Kineret) in patients with osteoarthritis of the knee [Abstract]. Arthritis Rheum 2005;54:S507.
65. Pandit H, Aslam N, Pirpiris M, Jinnah R. Total knee arthroplasty: the future. J Surg Orthop Adv 2006;15:79-85.
66. Brittberg M, Nilsson A, Lindahl A, Ohlsson C, Peterson L. Rabbit articular cartilage defects treated with autologous cultured chondrocytes. Clin Orthop 1996;326:270-283.
67. Wakitani S, Goto T, Pineda SJ, et al. Mesenchymal cell-based repair of large, full-thickness defects of articular cartilage. J Bone Joint Surg Am 1994;76A:57992.
68. Hangody L, Kish G, Karpati Z, Eberhart R. Osteochondral plugs: autogenous osteochondral mosaicplasty for the treatment of focal chondral and osteochondral articular defects. Operative Tech Orthop 1997;7:312-22.
69. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002;347:81-88.
70. Manusco CA, Ranwat CS, Esdaile JM, Johanson NA, Charlson ME. Indications for total hip and total knee arthroplasties. Results of orthopaedic surveys. J Arthroplasty 1996;1:34-46.
71. Dieppe P, Basler HD, Chard J, Croft P, Dixon J, Hurley M, et al. Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. Rheumatology 1999;38:73-83.
72. Abbaszade I, Liu RQ, Yang F, et al. Cloning and characterization of ADAMTS11, an aggrecanase from the ADAMTS family. J Biol Chem 1999;274:23443-50.
73. Tortorella MD, Burn TC, Pratta MA, et al. Purification and cloning of aggrecanase-1: a member of the ADAMTS family of proteins. Science 1999;284:1664-6.
74. Glasson SS, Askew R, Sheppard B, et al. Deletion of active ADAMTS5 prevents cartilage degradation in a murine model of osteoarthritis. Nature 2005;434:644-8.
75. Stanton H, Rogerson FM, East CJ, et al. ADAMTS5 is the major aggrecanase in mouse cartilage in vivo and in vitro. Nature 2005;434:648-52.
76. Noe MC, Natarajan V, Snow SL, et al. Discovery of 3-OH-3-methylpipecolic hydroxamates: potent orally active inhibitors of aggrecanase and MMP-13. Bioorg Med Chem Lett 2005;15:3385-8.
77. Saraf A, Mikos AG. Gene delivery strategies for cartilage tissue engineering. Adv Drug Deliv Rev 2006;58:592-603.
78. Bateman J. Genetic aspects of osteoarthritis. Semin Arthritis Rheum 2005;34:15-18.
79. Bau B, Gebhard PM, Haag J, Knorr T, Bartnik E, Aigner T. Relative messenger RNA expression profiling of collagenases and aggrecanases in human articular chondrocytes in vivo and in vitro. Arthritis Rheum 2002;46:2648-57.
80. Aigner T, Bartnik E, Zien A, Zimmer R. Functional genomics of osteoarthritis. Pharmacogenomics 2002;3:635-50.
81. Aigner T, Zien A, Gehrsitz A, Gebhard PM, McKenna L. Anabolic and catabolic gene expression pattern analysis in normal versus osteoarthritic cartilage using complementary DNA-array technology. Arthritis Rheum 200144:2777-89.

82. Gelse K, Aigner T, Stöve J, Schneider H. Gene therapy approaches for cartilage injury and osteoarthritis. Curr Med Chem 2005;4:265-79.
83. Fernandes JC, Tardif G, Martel-Pelletier J, et al. In vivo transfer of interleukin-1 receptor antagonist gene in osteoarthritic rabbit knee joints: prevention of osteoarthritis progression. Am J Pathol 1999;154:1159-69.
84. Zhang X, Mao Z, Yu C. Suppression of early experimental osteoarthritis by gene transfer of interleukin-1 receptor antagonist and interleukin-10. J Orthop Res 2004;22:742-50.
85. Evans CH, Gouze JN, Gouze E, Robbins PD, Ghivizzani SC. Osteoarthritis gene therapy. Gene Ther 2004; 11: 379-89.
86. Schiff MH, DiVittorio G, Tesser J, et al. The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. Arthritis Rheum 2004;50:1752-60.
87. Rudolphi K, Gerwin N, Verzijl N, van der Kraan P, van den Berg W. Pralnacasan, an inhibitor of interleukin-1beta converting enzyme, reduces joint damage in two murine models of osteoarthritis. Osteoarthritis Cartilage 2003;11:738-46.
88. Pelletier JP, Fernandes JC, Brunet J, Moldovan F, Schrier D, Flory C, Martel-Pelletier J. In vivo selective inhibition of mitogen-activated protein kinase kinase 1/2 in rabbit experimental osteoarthritis is associated with a reduction in the development of structural changes. Arthritis Rheum 2003;48:1582-93.
89. Ahmed S, Rahman A, Hasnain A, Goldberg VM, Haqqi TM. Phenyl N-tert-butylnitrone down-regulates interleukin-1 beta-stimulated matrix metalloproteinase-13 gene expression in human chondrocytes: suppression of c-Jun NH2-terminal kinase, p38-mitogen-activated protein kinase and activating protein-1. J Pharmacol Exp Ther 2003;305:981-8.
90. Ridley SH, Sarsfield SJ, Lee JC, et al. Actions of IL-1 are selectively controlled by p38 mitogen-activated protein kinase. Regulation of prostaglandin H synthase-2, metalloproteinases, and IL-6 at different levels. J Immunol 1997;158:3165-73.
91. Evans CH. Novel biological approaches to the intra-articular treatment of osteoarthritis. BioDrugs 2005;19:355-62.