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 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.”

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, 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{6} In 1995, the American College of Rheumatology (ACR) published recommendations for the medical management of OA of the hip and knee.\textsuperscript{7} Several therapeutic strategies have been developed for better medical treatments for OA.\textsuperscript{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.\textsuperscript{9}

<table>
<thead>
<tr>
<th>Criteria for Classification of Idiopathic Osteoarthritis (OA) of the Knee [1986]*</th>
<th>Clinical and laboratory</th>
<th>Clinical and radiographic</th>
<th>Clinical†</th>
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<td>Knee pain</td>
<td>Knee pain</td>
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<tr>
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<td>+ at least 1 of 3:</td>
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<tr>
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<td>– Stiffness &lt; 30 minutes</td>
<td>– Stiffness &lt; 30 minutes</td>
<td></td>
</tr>
<tr>
<td>– Crepitus</td>
<td>– Crepitus</td>
<td>– Crepitus</td>
<td></td>
</tr>
<tr>
<td>– Bony tenderness</td>
<td>+ Osteophytes</td>
<td>– Bony tenderness</td>
<td></td>
</tr>
<tr>
<td>– Bony enlargement</td>
<td>– Bony enlargement</td>
<td>– Bony enlargement</td>
<td></td>
</tr>
<tr>
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<td>– No palpable warmth</td>
<td>– No palpable warmth</td>
<td></td>
</tr>
<tr>
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<td>– ESR &lt; 40 mm/hour</td>
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</tr>
<tr>
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<td>– RF &lt;1:40</td>
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<tr>
<td>– SF OA</td>
<td>– SF OA</td>
<td>– SF OA</td>
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</tr>
</tbody>
</table>

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\textsuperscript{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\textsuperscript{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.\textsuperscript{10} Quadriceps weakness may be a risk factor for the development of knee OA, presumably by decreasing stability of the knee joint.\textsuperscript{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.\textsuperscript{12}

Decrease in proprioception, has also been documented in patients with knee OA.\textsuperscript{13,14} Hurley and Scott\textsuperscript{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.\textsuperscript{2}

Appetite suppressant and low-calorie diet is recommended for overweight patients with knee OA.\textsuperscript{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.\textsuperscript{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\textsuperscript{18} and equivalent to naproxen.\textsuperscript{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.\textsuperscript{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\textsuperscript{23} are less efficacious but better tolerated than high doses.\textsuperscript{24} Though the use of COX 2 inhibitors\textsuperscript{25} decreases the potential gastric toxicity of conventional NSAIDs, the results of recent trials showed increased cardiovascular risk with these agents limiting their use.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{31-33}

Glucosamine sulfate is more effective than glucosamine hydrochloride and taking chondroitin sulfate in combination with glucosamine sulfate may have an additive effect.\textsuperscript{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.\textsuperscript{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.\textsuperscript{35} These findings were also supported by two other studies conducted by Pavelka\textsuperscript{36} and Bruyere.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{40}
The recommended daily dose of diacerein for symptomatic relief of patients with knee OA is 50 mg twice daily.\textsuperscript{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.\textsuperscript{42}

**Antiresorptive Agents**

Recent research has highlighted the importance of subchondral bone as a target for therapeutic intervention and disease modification in OA.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{50} and an OA guinea pig model,\textsuperscript{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.\textsuperscript{5,52} Topical capsaicin reversibly desensitizes nociceptive C fibers by acting on the VR-1 vaniloid receptors.\textsuperscript{4}

Studies comparing diclofenac gel with ketoprofen gel\textsuperscript{53} and piroxicam gel with oral ibuprofen\textsuperscript{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.\textsuperscript{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. In clinical trials of intra-articular hyaluronan preparations, pain relief was significantly greater than that with placebo, and comparable with oral NSAIDs. Pain relief was also comparable with or greater than that with intra-articular glucocorticoids. Jubb and colleagues 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 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.

Corticosteroids
The pain and secondary inflammation in moderate to severe OA can be effectively relieved by intra-articular injection of steroids. 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. 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. Injection can be used as monotherapy 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.

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. However, another study did not confirm these results.

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.

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

Autologous chondrocyte transplantation, cartilage repair using mesenchymal stem cells, and autologous osteochondral plugs (mosaicplasty) 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.\textsuperscript{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.\textsuperscript{70-71}

\section*{FUTURE THERAPIES}

\subsection*{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.\textsuperscript{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\textsuperscript{74,75} A
selective inhibitor of aggrecanase and MMP-13 was recently reported.\textsuperscript{76} This therapeutic
approach may hold some promise for the future.

\subsection*{Gene Therapy}

Several candidate genes have been identified as potential targets for the treatment of OA,\textsuperscript{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.\textsuperscript{82}

Studies have shown beneficial effects of using different \textit{in vivo} gene therapy strategies with IL-1Ra in OA experimental models.\textsuperscript{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-\(\beta\) 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.

\subsection*{Targeting Synovial Inflammation: Interleukin-1\(\beta\)}

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

IL-1\(\beta\) is primarily synthesized as a precursor (pro-IL-1\(\beta\)), and must be cleaved by a cysteine-
dependent protease, named IL-1\(\beta\) 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-1\(\beta\) converting
enzyme inhibitor was found to reduce the progression of joint damage in two experimental
mouse models of OA.\textsuperscript{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.\(^8^8\) Recently it was reported that phenyl N-tert-butyl nitroxide, 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.\(^8^9\)

The p38 inhibitor has anti-inflammatory effects in cartilage explants and in animal models.\(^9^0\)

**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.\(^9^1\)

**REFERENCES**


