Management of Osteoarthritis: Can We Slow Disease Progression ?

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Summary

Guidelines for the Management of Knee OA (Pending a Disease Modifying Drug)

ACR (Arthritis Rheum 2000; 43:1905-1915) EULAR (Ann Rheum Dis 2003;62:1145-1155)

- *Tailor therapy and use combination approach*
- *Non-pharmacologic modalities important !*
- *Acetaminophen is first-line analgesic*
- *Intra-articular steroids - acute exacerbation*
- *NSAIDs for those that fail simple analgesics – Beware of those at risk for adverse events, consider topical*
- *Hyaluronic acid injections – efficacy ?*
- *Glucosamine and chondrotin sulfate – awaiting GAIT study*
- *Joint replacement for refractory pain associated with disability*

Introduction

The treatment goals for patients with any type of arthritis are to relieve pain, reduce inflammation, improve function, and ultimately halt disease progression. For osteoarthritis, we can reduce pain and improve function with a combination of non-pharmacologic and pharmacologic measures. However, we are still lacking treatments proven to slow disease progression. There is hope that as we gain a better understanding of the basic biology of osteoarthritis that we will find new therapeutic targets which will meet this goal. Until then, the current management of osteoarthritis should be tailored to the individual patient and should be designed to reduce pain and improve function with the lowest chance of producing serious side-effects. In part, the choice of treatment will depend on the degree of joint damage, which in OA can range from mild to severe. For mild cases non-pharmacologic measures and simple analgesics are often sufficient while in advanced cases joint replacement surgery is still the mainstay of treatment.

The Combination Approach to the Management of OA

It has become clear that no single treatment for OA, given alone, is of much benefit. The approach to management should be multi-disciplinary and include the primary care physician, occupational and physical therapists, dieticians, and orthopaedic surgeons in addition to a rheumatologist when needed (Figura 1).

Disease-Modifying Drugs for OA (DMOADs)

The class of drugs known as disease-modifying (or structure-modifying) drugs includes agents which prevent, retard progression of, or reverse morphologic changes in patients with OA. A number of agents have been tested which would fit in this class, although none have been conclusively proven to be true DMOADs. Some important questions must be addressed as we develop and test such agents. These questions include: who to treat, when to start (and stop) treatment, how to decide if it is working, and what to do if an agent prevents structural progression without improving pain or function. It seems most likely that DMOADs will need to be started at early time points in the disease before significant joint damage has occurred. There is much less chance to affect advanced stages of OA. It is hoped that the use of MRI and perhaps OA

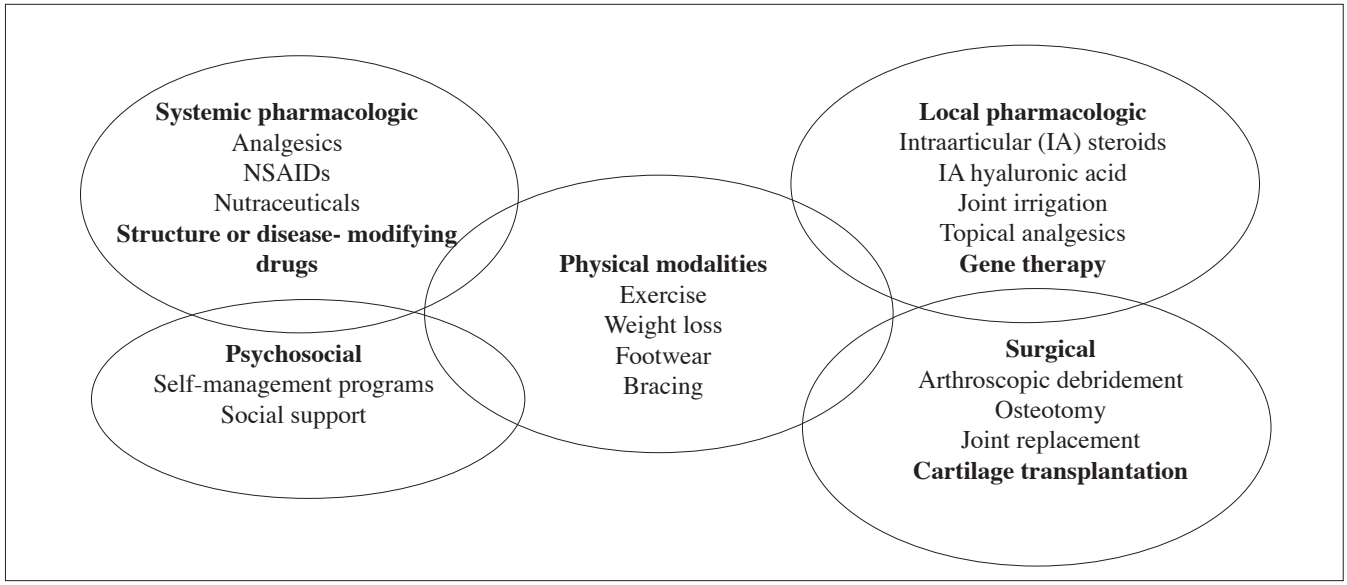

Figura 1.

biomarkers and genetics will help identify the correct patients for DMOADs but this approach is still experimental. DMOADs may be designed to target the synovitis in OA, the bone, or the cartilage but if the biomechanical factors are not addressed then such treatments may fail or will have much less impact on disease progression.

Bone as a Target for OA

Because bone changes are so prominent in OA, there is interest in developing agents which may slow OA by affecting bone turnover. In animal models estrogen replacement reduces OA but it is not clear if this is due to an affect on bone or cartilage. Bisphosphonates have also been tested successfully in animal models but the initial clinical trials in humans have been disappointing. Finally, calcitonin has also been shown to be of benefit in animal models of OA but trials in humans have not been reported.

Potential DMOADs

A number of agents have been tested or are under active investigation. These include: Tested

- Glycosaminoglycan polysulfate (Arteparon)
- Glycosaminoglycan peptide complex (Rumalon)
  – Not effective in a 5yr study of knee or hip OA (Osteoarthritis Cart 2000)
- Diacerin
- Sodium pentosan polysulfate
- Doxycycline
- Glucosamine and chondroitin sulfate

Under investigation

- Il-1 inhibitors- IL-1 receptor antagonist, IL-1 converting enzyme (ICE) inhibitors
- IGF-I and BMPs
- MAP kinase inhibitors
- Anti-oxidants

Diacerin is thought to act by inhibiting IL-1 synthesis and activity. It has shown some efficacy in reducing joint space loss in hip OA but less affect on symptoms and is associated with a significant degree of diarrhea. Doxycycline has been shown to inhibit MMP activity in vitro and in vivo. It was affective in a dog model of OA. In a recent human randomized controlled 30-month trial it was shown to modestly reduce x-ray progression in obese women with grade 2-3 (on a 0-4 scale) OA but did not prevent the development of early OA in the opposite knees of the same subjects (which is what the trial was designed to do). It appears that further studies of doxycycline are needed but it may be useful in patients with aggressive erosive OA.

Sodium pentosan polysulfate (synthetically sulfate xylan from hemicellulose) is a serine protease inhibitor which has shown some efficacy in animal models but data in humans is lacking. The efficacy of glucosamine and chondrotin sulfate has been demonstrated in some

studies but not confirmed in others. A large multi-center US study is currently being completed and should provide further evidence on the future role of these compounds as DMOADs. Observational studies have suggested that low intake of vitamin C and vitamin D is associated with OA progression but randomized clinical trial data is not available to know if vitamin supplements are helpful. In theory, weight loss in overweight and obese patients might slow disease progression but this is unproven. Weight loss has been shown to reduce pain and improve function (discussed below).

Non-pharmacologic management of OA

Even if we can develop agents which slow or halt disease progression in OA, it will still be important to include non-pharmacologic measures designed to improve biomechanics and function. Muscle weakness and aerobic deconditioning are common features of OA and should be managed with exercise therapy. Many studies have shown the benefits of both aerobic and muscle strengthening exercises for OA patients. The exercise prescription should be tailored to the individual patient after assessing the stage of the disease and other co-morbidities. For example, patients with mild to moderate OA benefit from a walking program combined with resistance training while patients with advanced disease may tolerate water exercises but not weight-bearing exercise. A dietary weight loss intervention has been shown to be of benefit for overweight and obese adults with OA. Patients who adhere to the diet and exercise plan clearly do the best and the health care team needs to find ways to keep patients motivated and involved in their care.

Other non-pharmacologic measures include knee braces for uni-compartmental OA designed to reduce loads on one side of the joint. Lateral heel wedges which insert into the shoes may also benefit OA patients who have primarily medial joint disease. Medial taping of the patella can be helpful for patellofemoral OA.

Analgesics for OA

The recent problems with certain COX-2 inhibitors have served to re-emphasize the fact that since none of these agents are a "cure" for OA and the pain relief is pretty similar among all analgesics, safety should be a major concern. In many patients simple analgesics such as acetaminophen are still of value. Often analgesics need to be combined to give better pain relief. NSAIDs and acetaminophen can be used together or either of these can be used with centrally acting agents such as tramadol or inpatients with advanced disease with opiods.

Other OA treatments

Corticosteroid injections have benefit in reducing pain when compared to placebo but only for about 4-6 weeks. Hyaluronate injections may give longer-term relief in some patients but overall the efficacy is not much greater than placebo. Arthroscopic debridement is not of benefit (at least in patients that don't have significant mechanical complaints). Tibial osteotomy is still useful for uni-compartmental involvement as a means to delay joint replacement surgery. Joint replacement is still the best treatment for advanced disease. Cartilage or chondrocyte transplantation is being developed but not close to being ready for OA patients.

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