

DRUG THERAPY IN KNEE OSTEOARTHRITIS

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ABSTRACT

Clinical treatment for osteoarthritis (OA) is very important and is based on patient's self care and guided by the physician. Drug therapy is additional to losing weight, improving muscular strength, proprioception, flexibility and range of motion. Between the available drugs for osteoarthritis' treatment, some are basically analgesics and do not interfere on disease's progression; some are anti-inflammatory with good analgesic power but with side effects that compromise their prolonged usage; and the structure modifying drugs that slow down the progression of OA. The medications are presented in topic,

oral, intra-muscular, intra-venous and intra-articular forms. The hyaluronic acid has various presentations with good analgesic effect and some evidence of structure modifying property. There is IA evidence level for the use of diacerhein and of glucosamine to slow down the disease. Still, more technology for diagnosis and therapy control of OA is necessary to define the efficacy of other drugs.

Keywords – Osteoarthritis; Anthraquinone; Glucosamine; Chondroitin; Hyaluronic acid

INTRODUCTION

Until a few decades ago, the treatment of osteoarthritis or osteoarthrosis (OA) was limited to the use of simple analgesics, anti-inflammatory drugs, physical measures (weight loss, muscle strengthening, and physical therapy modalities), infiltration with corticosteroids and, in refractory and more serious cases, surgical treatment. The progressing understanding of the pathophysiology of osteoarthritis in the knee, the perception that the process is not purely mechanical and/or an aging process, and the elucidation of the inflammatory pathways involved led to the clinical application of many other medications. Although a cure for osteoarthritis is still beyond the reach of medicine, there has been discussion regarding

the existence of disease-modifying drugs, which have the ability to alter the course of joint degeneration, slow its progression, and possibly make it asymptomatic, thereby avoiding a portion of protective surgical procedures.

Since researchers expect that if medication can slow the disease, it can also render it asymptomatic, most of the studies with structure-modifying drugs are of short duration and compare them with fast-acting analgesic drugs. OA is a disease of slow evolution. Radiographic changes take three years to be observed/measured. The very loss of knee joint space is more related to the extrusion of the meniscus than the loss of femoral-tibial cartilage.

Over the years, researchers have learned that pain in OA can be controlled without intervening in the

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disease process. The opposite also occurs. You can intervene in the process of OA without resolving all of the pain. The pain is multifactorial and is also related to the degree of OA.

Markers of OA (in blood and urine) are being researched, particularly to assess if the arthritis is progressing or is under control.

In this update, we will discuss primarily the medications that are considered structure-modifiers in the disease and what level of evidence supports their use.

PATHOPHYSIOLOGY OF OA

Although OA is a disease of the entire joint (cartilage, ligaments, synovium, and bone), the initial lesion is usually in the articular cartilage. OA has a strong genetic component and, in most cases, has mechanical overload as an initiator of the process of cartilage damage, which evolves to a vicious inflammatory cycle, perpetuating joint degradation. This inflammatory pathway has as its primary agents interleukin-1 (IL-1) and tumor necrosis factor (TNF), which induce increased expression of metalloproteinases and nitric oxide (NO), the main catabolic agents produced by chondrocytes in response to injury, in addition to more IL-1. Treatment of osteoarthritis can target both the mechanical overload that leads to joint damage and the inflammatory cycle that perpetuates the injury at one or more points in this chain.

To facilitate the study of the medication options used in osteoarthritis, it is customary to divide drugs into two main groups: fast-acting symptomatic drugs and slow-acting drugs. Among the latter are the structure-modifying drugs (which also include fast-acting analgesic drugs and those of prolonged action), which are discussed below. It should be remembered that drug therapy has to be seen as a complement, and not a replacement, for non-drug therapy. The primary objective of conservative treatment of OA is self-care (weight loss and motor control)⁽¹⁾.

SPECIFIC DRUGS FOR THE TREATMENT OF OA

Within this group are the medications that act more specifically in the disease process of osteoarthritis, having in theory the ability to be disease-modifying (preventing, slowing, reversing, or stabilizing the alteration of joint structure). There is evidence to suggest that some of these drugs are structure modifiers.

HYALURONIC ACID

Synovial fluid in OA shows reduced viscoelasticity^(2,3). For the lubrication and protection of cells and joint tissues, high viscoelasticity is essential. Thus, one of the causes of pain and decreased joint mobility may be the decrease in the protective effect of this viscoelastic medium through the pain receptors in the synovial tissue⁽⁴⁾. Viscosupplementation is a relatively new therapy that acts directly on the causes of pain and stiffness in OA, replacing the synovial medium with low viscoelasticity with a highly viscoelastic hyaluronic acid solution⁽⁵⁻⁷⁾.

There are various preparations of hyaluronic acid on the market and their different rheological properties are primarily dependent on their molecular weights⁽⁸⁾. With a molecular weight of 6×10^6 daltons (Da), the viscoelastic properties of hylan GF 20 are similar to the synovial fluid of healthy young adults⁽³⁾; three weekly injections have been proven to be safe and superior in efficacy compared to placebo (infiltration of saline solution or arthrocentesis)^(9,10) with analgesia up to six months. With a molecular weight of 500-730kDa, the viscoelastic properties of sodium hyaluronate (Na-HA) are smaller than those of normal synovial fluid, but proved to be viscosity inducers (i.e., inducing the synovium to produce hyaluronic acid of higher molecular weight)⁽¹¹⁾. The results of these preparations with lower molecular weight compared with injection of saline or arthrocentesis vary, sometimes revealing a statistical difference, sometimes revealing no difference⁽¹²⁻¹⁴⁾.

Studies comparing the high molecular weight preparation (hylan GF 20) with other low weight preparations have been published in recent years, with varying results. Some showed no statistical difference⁽¹⁵⁾, while others showed greater efficacy in the compound with high molecular weight⁽¹⁶⁻¹⁸⁾, and others still showed a greater efficacy in the compound with low molecular weight^(11,19,20). Another study showed a similarity between treatment with hyaluronic acid and treatment with only physical measures/physical therapy⁽¹⁸⁾. A recent meta-analysis⁽²¹⁾ showed that the use of hyaluronic acid has little effect compared to intra-articular placebo and that compounds with high molecular weight tend to have better results (faster and prolonged analgesia in OA).

Hyaluronic acid may have a structure-modifying effect. A randomized study⁽²²⁾, in which patients underwent knee arthroscopy at the beginning and end of

one year of treatment with four series of three weekly injections of hyaluronic acid ($6-8 \times 10^5$), showed less deterioration of the cartilage and more organelle synthesis in cartilage treated with hyaluronic acid than in the cartilage of those injected with saline. A prospective, randomized, blind study⁽²³⁾ showed no radiological difference between the placebo and the medication in one year, although the time was too short to evaluate radiological differences in a method for treating osteoarthritis. However, it was noted that separating only the group of patients with the largest joint space (less severe osteoarthritis, where there are more chondrocytes to be influenced or not by the drug), hyaluronic acid showed significantly better results. Possible complications are infection (risk similar to the injection of corticosteroids) and local inflammatory reaction that occurs in up to 3% of cases, with symptoms lasting up to three weeks.

Thus, there is evidence of the good and prolonged analgesic effect of hyaluronic acid, and that the higher the molecular weight, the greater its analgesic power. What molecular weight would best preserve the articular cartilage is not known with certainty. Some animal studies tend to suggest that a molecular weight between 0.6 and 1.0×10^6 Da would best stimulate the production of the matrix components, which may be partially explained by the fact that the lower molecular weight would more easily penetrate the extracellular matrix, maximizing concentration, and also facilitating its interaction with target cells of the synovium. In addition, there is evidence that the binding of hyaluronic acid molecules with cell receptors is dependent on the molecular weight⁽¹¹⁾. Studies show that high molecular weight HA also stimulates synthesis organelles⁽²⁴⁾. This observation of which molecular weight better protects articular cartilage in animals has not been tested in humans⁽¹¹⁾. There are preparations that are taken from the crest of the rooster; patients allergic to bird products should not be injected with such preparations. There is hyaluronic acid produced by fermentation, which has a lower molecular weight, albeit without the problems of allergens or cross-links between molecules of hyaluronic acid that can lead to synovitis during the process of breaking these cross-links.

Hyaluronic acid should not be injected into knees with synovitis. The synovitis should be first treated or punctured, and can be injected with the first vial of hyaluronic acid into 1 ml of triamcinolone⁽²⁵⁾.

DIACEREIN

It acts mainly by inhibiting the effects of IL-1 that degrades the protein inhibitor of nuclear factor kappa-beta, which leads to transcription of nitric oxide, IL-1, TGF, and metalloproteinases⁽²⁶⁻²⁹⁾, and also has anabolic properties, stimulating the production of TGF-B and proteoglycans, collagen, and hyaluronic acid⁽³⁰⁾. Besides its effectiveness in relieving symptoms of osteoarthritis, its disease-modifying action by its smaller decrease of joint space relative to placebo has been proven in a long-term (three years), multicenter, prospective study. That is, level of evidence IA that it is a disease-modifying osteoarthritic drug, delaying the development of OA⁽³¹⁾. The recommended dosage is 100 mg/day⁽³²⁾, attention should be given to the possible side effect of altering intestinal peristalsis. It can be administered to patients with renal or cardiac insufficiency^(31,32).

GLUCOSAMINE

Glucosamine participates in the synthesis of glycosaminoglycans (GAGs), proteoglycans, and hyaluronate in articular cartilage, although the exact mechanism has not yet been elucidated⁽³³⁾. In addition to functioning as a substrate, it acts directly on chondrocytes, stimulating the synthesis of proteoglycans and inhibiting the synthesis of metalloproteinases. It inhibits the effects of IL-1 on nuclear factor kappa-beta in the chondrocyte layer, also inhibiting the production of nitric oxide, more IL-1 and TGF. It acts on osteoclasts and the synovium⁽³⁴⁾.

Recent meta-analysis showed that the drug has superior efficacy to placebo, and that, in addition to symptomatic improvement, it decreases the effect of joint narrowing⁽³³⁻³⁶⁾. There are three types of glucosamine in the market. Glucosamine hydrochloride (HCl – removed from crab shells), glucosamine sulfate (taken from the shells of deep-water shrimp), and synthetic glucosamine (sulfate). There is level of evidence IA that synthetic glucosamine slows the development of OA (continuous use for three years)⁽³⁷⁾ and this effect is maintained even five years after cessation of drug use⁽³⁸⁾. Its dosage is simple. The dose is 1500 mg daily. In the case of synthetic glucosamine, this dose leads to a concentration of $10\mu\text{Mol}$ in the blood and synovial fluid (minimum therapeutic dose of glucosamine). Glu-

cosamine hydrochloride, given at a dose of 500 mg three times a day, reaches a concentration of 3µMol in the synovial fluid (less than the therapeutic dose)^(39,40).

CHONDROITIN

Chondroitin sulfate is a GAG found in various human tissues, including hyaline cartilage. Studies show, in addition to direct stimulation of cartilage, its inhibiting action on IL-1 and metalloproteinases^(41,42). Chondroitin is a large molecule, which is broken when absorbed by the intestine. There is glucosamine in its formation.

Recent meta-analysis showed that the drug has efficacy superior to placebo, with symptom relief as its predominant effect, without reducing the joint narrowing of glucosamine^(33,35,36,43).

The recommended dose is 1200 mg/day.

COMBINATION OF GLUCOSAMINE AND CHONDROITIN

The combination of drugs, acting in different ways with complementary effects, would be better than isolated use. The usual dosage is 1500 mg of glucosamine and 1200 mg of chondroitin in single or divided daily dose, depending on the commercial composition. It shows good tolerance to prolonged use with few side effects.

The GAIT study (Glucosamine HCl/chondroitin Arthritis Intervention Trial), multicenter, double-blind, randomized, with placebo- and celecoxib-(selective NSAID COX-2 inhibitor) controlled groups, was recently published⁽⁴⁴⁾. The study included 1583 patients, and results after 24 weeks showed that in the general group the combination of drugs, from the standpoint of analgesia, was not superior to placebo, whereas celecoxib was. Separating only patients with moderate to severe pain, there was statistical difference compared to placebo, suggesting greater benefit in this patient group.

AVOCADO AND SOYBEAN UNSAPONIFIABLES

They are proven inhibitors of IL-1, IL-6, IL-8, and metalloproteinases in vitro⁽⁴⁵⁾ and chondrocyte stimulators in vitro⁽⁴⁶⁾.

A review article of four randomized, double-blind,

placebo-controlled studies showed improvement of symptoms in three; however, the only long-term study among these showed negative results for hip osteoarthritis, but positive results for knee OA⁽⁴⁷⁾. A recent meta-analysis (2008) of controlled studies with soybean and avocado unsaponifiables showed that their use reduces pain, reduces the intake of analgesics, and improves function in patients with knee OA⁽⁴⁸⁾. Nevertheless, the ability of this drug to prevent joint space loss in osteoarthritis is not yet clear. A prospective randomized study evaluating the hip joint space after using the medication showed significant results only in the subgroup with advanced osteoarthritis, without significant results in the study population as a whole⁽⁴⁹⁾.

With a dose of 300 mg/day, the Brazilian consensus on OA (OARSI) indicates the use of soybean and avocado unsaponifiables for the treatment of OA.

CHLOROQUINE

It shows a suppressive effect in the NO production induced by IL-1⁽⁵⁰⁾.

Its clinical efficacy in the treatment of osteoarthritis has not been established; however, it seems to be particularly useful in inflammatory and erosive forms of osteoarthritis. In Brazil, there is a consensus statement (OARSI) for chloroquine as a treatment option for OA.

OTHER DRUGS

Many other substances of natural and synthetic origin have been studied for their supposed antiarthritic effects. Even gene therapy has been investigated for application in the treatment of osteoarthritis.

We should continue to expect much in the future of the clinical treatment of osteoarthritis.

FINAL CONSIDERATIONS

As we have seen, there are several medications available with the potential to modify the progression of osteoarthritis by acting directly on the pathophysiology of the disease. Nevertheless, based on scientific evidence, one can conclude that:

- Hyaluronic acid improves pain and function for patients with osteoarthritis;
- Diacerein and synthetic glucosamine slow the progression of osteoarthritis.

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