

TREATMENT OF OSTEOARTHRITIS

There are three basic objectives of osteoarthritis treatment:

- Relieving pain and discomfort
- Minimizing functional impairment
- Delaying the progression of the process

The substances considered to be effective in the treatment of osteoarthritis can be classified as slow-acting or fast-acting symptomatic drugs and/or disease-modifying drugs (5).



Fig. 1. Diagram of the kinds of osteoarthritis treatment and how they act

OSTEOARTHRITIS		
PHYSIOPATHOLOGICAL	CLINICAL	
Cartilage Destruction	Inflammation Mediators	Pain Functional Impairment
STRUCTURE-MODIFYING TREATMENT	SYMPTOMATIC TREATMENT	

A. Fast-acting and slow-acting symptomatic drugs

A.1. Fast-acting symptomatic drugs

This group of drugs, which includes analgesics, NSAIDs, corticosteroids, etc., has been used for years to improve the signs and symptoms associated with pain, functional impairment, mobility, etc.

These drugs provide a number of advantages derived from the fact that they improve painful symptoms quickly and powerfully. However, they have certain drawbacks. They cannot modify the evolution of the disease, the symptoms may reappear when treatment is

suspended, they are not free of safety problems (for the gastrointestinal, cardiovascular, hepatic and renal systems) and can cause interaction problems with other drugs. Moreover, it is sometimes necessary to take them in association with gastroprotective agents.

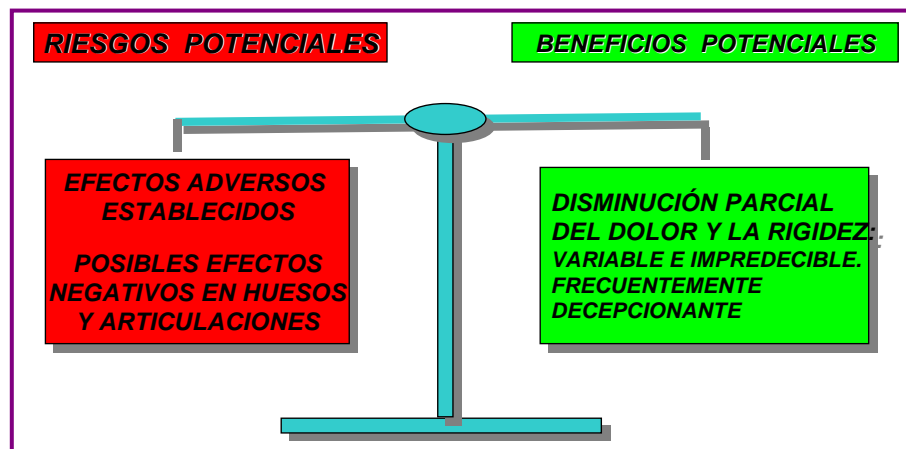


Fig. 2. Risks vs. benefits in the prescription of NSAIDs for osteoarthritis.

POTENTIAL RISKS	POTENTIAL BENEFITS
ESTABLISHED ADVERSE EFFECTS POSSIBLE NEGATIVE EFFECTS ON BONES AND JOINTS	PARTIAL REDUCTION OF PAIN AND RIGIDITY IS VARIABLE AND UNPREDICTABLE. FREQUENTLY DISAPPOINTING

A. 2. Symptomatic slow-acting drugs

Although symptomatic slow-acting drugs for osteoarthritis (SYSADOA) respond slower than NSAIDs, their clinical efficacy gradually increases until it reaches an overall efficacy level comparable to that of NSAIDs (3,4). This reduction of symptoms lasts longer and may even persist some months after treatment has stopped, as has been reported for hyaluronic acid (4), chondroitin sulfate (3) and glucosamine sulfate (5). All three have the added advantage of being safer than NSAIDs (3,4).

Although a number of different substances behave like SYSADOA (6,7), considerable clinical experience has been gained primarily with hyaluronic acid (intra-articular route), and chondroitin sulfate and glucosamine sulfate (taken by mouth).

► Chondroitin sulfate

Chondroitin sulfate (CS) forms part of the group of glycosaminoglycans, which are important structural components of the extracellular matrix of cartilage. CS is mainly present in the cells surrounding the extracellular matrix and is more abundant in tissues with a large extracellular matrix, such as those that form connective tissues in the body, cartilage, skin, blood vessels, ligaments and tendons (8).

In degenerative joint diseases such as osteoarthritis, there is deterioration and loss of articular cartilage. A key phase in the degenerative process is the loss of proteoglycan in the cartilage and the exposure of the collagen network to mechanical malfunction (7).

Clinical trials on osteoarthritic patients have shown that treatment with **CS reduces or stops osteoarthritis symptoms such as pain and functional impairment, and improves the movement of affected joints for 2 or 3 months.**

Because it is a SYSADOA, **CS takes about 2 or 3 weeks to start acting, though it eventually reaches the same efficacy level as NSAIDs. Moreover, it has a residual effect through which its efficacy is maintained for up to 2 to 3 months after treatment is discontinued** (3, 10).

In total, eleven randomized, double-blind clinical trials compared the effect of CS and placebo in 1024 patients with osteoarthritis of the knee, hip and fingers who were treated for periods ranging from 3 to 36 months (3, 9, 10, 12-19).

The results of all these clinical trials concluded that **CS is more effective (approximately 50% more, $p < 0.05$) than placebo in reducing spontaneous pain, increasing functional capacity, reducing the amount of rescue medication taken, and in the global assessment of the patient and the researcher.**

The excellent safety demonstrated in all the clinical research done with CS is of special interest in chronic treatment (continuous treatment and/or treatment in cycles), as in the case of osteoarthritis (3, 11-15).

► **Glucosamine Sulfate**

Glucosamine sulfate (GS) is an active ingredient of biological origin present in the human organism and synthesized from chitin extracted from the shells of crustaceans.

Glucosamine is a natural aminomonosaccharide and is the substrate for the biosynthesis of cartilage proteoglycans.

Because it is a SYSADOA, **glucosamine takes about 2 or 3 weeks to start acting, though it eventually reaches the same efficacy level as NSAIDs. Moreover, it has a residual effect through which its efficacy is maintained for up to 2 months after treatment is discontinued** (3, 10).

► **Hyaluronic acid**

Hyaluronic acid (AH) belongs to the glycosaminoglycan family and is found in different extracellular tissues, including the synovial fluid, the extracellular matrix of the skin and the cartilage.

Hyaluronic acid **gives viscoelasticity to synovial fluid, which is fundamental for its lubricating and cushioning properties, and essential for the proper structure of the proteoglycans in the articular cartilage.** In osteoarthritis, the amount of hyaluronic acid in the synovial fluid and the cartilage is insufficient and its quality is altered.

Intra-articular administration of HA improves the mobility of joints with degenerative cartilage on the joint surface and synovial-fluid disorders. There are several forms of

hyaluronic acids that have different clinical effects, depending on the source, concentration, dosage and, especially, molecular weight (1).

B. Drugs that modify the course of osteoarthritis

When we talk about drugs that can modify the course of osteoarthritis, we are referring to the structure/disease modifying osteoarthritis drugs (S/DMOADs) (2, 20) or simply structure-modifying drugs (21). This group includes agents capable of preventing, delaying, stabilizing, repairing and/or reversing the symptoms of the disease in the form of lesions of the bone and cartilage (5).

Clinical trials on chondroitin sulfate (14,15,17,18,19), glucosamine sulfate (22,23) and hyaluronic acid (24,25) have shown for the first time that these substances are not only SYSADOA, but may affect the course of the disease (by slowing down or delaying development of the disease).

▶ *Chondroitin sulfate*

Clinical evidence has been obtained in three clinical trials carried out on osteoarthritis of the knee (14,17,18) and two clinical trials involving patients with osteoarthritis of the fingers (15,19).

In patients with osteoarthritis of the knee, **treatment with CS was shown to be associated with stabilization of the joint space, whereas joint-space narrowing was observed in the group of patients treated with placebo.** It was therefore concluded that treatment with CS can delay the progress of osteoarthritis. With regard to the results of the OA of the fingers, it was concluded that **osteoarthritis was less progressive in patients treated with CS and fewer patients in the CS group developed erosive osteoarthritis.**

The results are of great interest and made it possible to come to the conclusion that **treatment with CS can limit the evolution of osteoarthritis and is also effective against associated signs such as pain and functional impairment.**

▶ *Glucosamine sulfate*

In two comparative clinical trials with placebo in osteoarthritis of the knee, **significant joint-space narrowing was observed in the placebo group, whereas there was no narrowing among the patients treated with GS (22,23).**

▶ *Hyaluronic acid*

Preliminary clinical results (24,25,26) confirm some of the work done in experimental pharmacology (27,28) and appear to indicate that intra-articular HA can halt the osteoarthritic process.

Conclusion

All the data reviewed seem to indicate that we are entering a new era for the treatment of osteoarthritis with a more natural pharmacological approach that bears in mind the physiopathology of the disease and the role these substances can have in the prevention of damage to the cartilage and treatment. Moreover, the safety demonstrated by these substances may result in an improvement to the quality of life of patients with osteoarthritis and a major reduction in the costs this disease generates in society.

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