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Editorial

Current Status of Symptomatic Slow-acting Drugs for Osteoarthritis (SYSADOAs) in Spain☆

Situación actual de los SYSADOA en España

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Osteoarthritis is characterized by the degeneration and loss of joint cartilage. It is associated with hyperostosis (formation of osteophytes and subchondral bone sclerosis) and frequently with low-grade fever. The clinical features are pain, sensitivity, stiffness and crepitus in the affected joint, occasional effusion, and varying degrees of local inflammation. These changes result in functional limitation and a reduced quality of life.[1]

Osteoarthritis can occur in any joint, but us most common in hips, knees, hands, feet and spine. It is the most widespread cause of chronic pain and disability in older individuals. The diagnosis of osteoarthritis is based on the clinical signs and radiological findings, although there is not always a good correlation between the two assessments.

According to the ArtRoCad (Osteoarthritis in Knee and Hip) study,[2] the mean annual cost of knee and hip osteoarthritis in Spain amounts to € 1502 per patient, for a total cost of € 4738 million/year, that is, the equivalent to 0.5% of the Spanish gross domestic product. The direct costs range between € 40 and € 18,155 a year per patient. Regarding direct costs, the major part of the budget (47%) is allocated to medical expenses, especially the time spent by specialists in attending to patient visits (22%) and hospital admissions (13%). However, pharmaceuticals account for only 5% of the costs.

Traditionally, the treatment strategy has targeted pain relief and control using analgesics and nonsteroidal anti-inflammatory drugs (NSAID). The most widely employed analgesic has been paracetamol, but recent evidence of its toxicity[3] and inefficacy in the treatment of osteoarthritis[4] have led some authors to question its utility. Recently, Roberts et al.[3] published a systematic review in which they demonstrate a relationship between paracetamol intake at the recommended analgesic doses and the incidence of adverse cardiovascular, gastrointestinal and renal effects in adults and, what's more, an increase in the rate of mortality. On the other hand, compared with placebo, doses of 3000–4000 mg/day of paracetamol produce slight, short-term pain reduction and disability in patients with osteoarthritis of the knee or hip.[4] The evaluation of the adverse effects indicates that patients who take paracetamol quadruple their likelihood of having abnormal results on liver function tests compared to those taking placebo.[4]

The toxicity of NSAID in the gastrointestinal tract is well known, and there are increasing warnings about the secondary effects associated with these drugs. Thus, patients are recommended to use them at the lowest dose and over the shortest possible period of time, and never as chronic treatment. In April 2015, the Spanish Agency of Medicines and Health Products (AEMPS) endorsed the recommendations of the European Pharmacovigilance Risk Assessment Committee (PRAC) and advised against administering high doses of ibuprofen (≥2400 mg/day) or dexibuprofen (≥1200 mg/day), as they are associated with a higher risk of arterial thrombosis, comparable to cyclooxygenase-2 (COX-2) inhibitors at standard doses.[5] The United States Food and Drug Administration (FDA) has requested the update of NSAID labels to ensure that they indicate that these drugs increase the risk of myocardial infarction, and recommends that physicians remain alert to the possible presentation of adverse effects in patients who are receiving them. The FDA also advises patients who take NSAID to seek medical attention immediately if they experience the symptoms of myocardial infarction or stroke, such as chest pain, weakness, numbness or paralysis of any part of the body, difficulties in speaking or comprehension, and/or respiratory insufficiency.[6]

The results of certain clinical trials suggest that treatment with symptomatic slow-acting drugs for osteoarthritis/disease modifying osteoarthritis drugs (SYSADOA/DMOAD) reduces pain and stiffness and increases functional capacity in patients with moderate to severe osteoarthritis,[7–9] even at the level of mechanisms of action.[10] The Glucosamine/Chondroitin Arthritis Intervention (GAIT) Trial,[11] one of the largest trials conducted to date with these drugs, involved 1583 patients with knee osteoarthritis. It compared the drugs with placebo and celecoxib, and found no statistically significant effect for chondroitin sulfate (CS) or glucosamine hydrochloride, alone or in combination, after 6 months of treatment. The authors attributed these results in part to the elevated response rate in the placebo group (60%) and to the fact that the majority of the participants had mild pain at the start and, thus, a narrow margin for discernible improvement. On the other hand, in this trial, the analysis of the patients with moderate to severe pain did reveal a statistically significant effect for the combination

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of CS and glucosamine in terms of pain and functional capacity, among other parameters.

In the continuation of the GAIT trial,[12] which included 662 of the initial 1583 participants, in whom the study was prolonged until the patients had completed 2 years of treatment, no significant differences were observed with respect to placebo for any of the treatment groups. Nor were significant differences found for the positive control using celecoxib, although there was an overall drop-out rate of around 50%, a circumstance that may have seriously compromised the statistical power of the study for the detection of significance.[12]

Gabay et al.[7] demonstrated that, after 6 months of treatment with CS, the patients with severe symptomatic hand osteoarthritis reported a reduction in the pain and in morning stiffness, in addition to improvement in functional activity, and experienced no important adverse effects.

Singh et al.,[8] authors of an extensive Cochrane review published in 2015, concluded that CS alone or in combination with glucosamine in patients with osteoarthrosis was superior to placebo, producing a statistically significant clinical improvement in joint pain. The findings in both the overall physical evaluation scores, like the Lequesne index, and the less marked reduction of the joint space width were better in the treatment groups than in the patients receiving placebo. The risk of serious secondary effects was lower in the group with CS than in the groups receiving other control drugs.[8]

The treatment of osteoarthritis with SYSADOA has as strong an effect as treatment with celecoxib, as was demonstrated in the Multicentre Osteoarthritis intervention trial with SYSADOA (MOVES).[9] After 6 months of treatment with CS + glucosamine hydrochloride, the patients with knee osteoarthritis and moderate to severe pain experienced pain relief, reduced stiffness, inflammation and joint effusion, and increased mobility. These results confirm the observation that the combination of CS + glucosamine hydrochloride constitutes a therapeutic alternative for the patients with comorbidities and, thus, taking multiple medications, given that the safety profile is superior to that of NSAID.[9]

The authors of a recently published clinical trial[13] observed a reduction in the narrowing of the joint space measured in patients with knee osteoarthritis who received CS + glucosamine sulfate for 2 years, compared to placebo. Both this group of patients and those who received only CS, glucosamine sulfate or placebo reported a reduction in knee pain after 1 year of treatment.

The controversy arises with studies like the meta-analysis published in the British Medical Journal,[14] which concludes that neither CS nor glucosamine, nor the combination of the two, are clinically effective in the treatment of osteoarthritis. That study was the object of several letters to the editor in which there were comments on the methodology used, mainly concerning the inclusion of studies in which the only aim was to assess the modifying effect of the drugs (in patients with little pain) to determine their effects on the symptoms. The editors of the British Medical Journal themselves published an online communiqué in which they retracted some of the affirmations in the article and suggested that some of the conclusions could have been erroneous or biased.

A more recent meta-analysis[15] that also analyzes the effect of chondroitin and glucosamine, alone and in combination, concludes that the 3 alternatives produce clinically significant pain relief in osteoarthritis. The authors also question the conclusions of the aforementioned meta-analysis of Wandel et al., citing methodological biases.

In Spain, the VECTRA (Valoración Económica y Sanitaria de Condroitín Sulfato en el Tratamiento de la Artrosis) study (*Economic Evaluation of Chondroitin Sulfate and Non-steroidal Anti-inflammatory Drugs for the Treatment of Osteoarthritis*) demonstrated that the treatment of osteoarthritis with CS is associated with lower costs and a better gastrointestinal tolerance than NSAID, which results in a decrease in the use of gastroprotective agents.[16]

Chondroitin sulfate and glucosamine have different mechanisms of action that explain why the combined treatment is more effective than the use of each drug alone. The absorption of CS is immediate and is produced in the segment proximal to the small intestine, and its highest plasma concentration is found 2–3 h after administration. When it reaches the joint, it is distributed in cartilage and subchondral bone tissue, but its penetration in chondrocytes is limited. It is most effective in the early stages of osteoarthritis, when fragments of the extracellular matrix trigger the inflammatory response. Chondroitin sulfate has been shown to reduce synovitis and subchondral bone lesions.[10] Concerning the importance of the use of the two glucosamine salts, glucosamine sulfate and hydrochloride, the European Medicines Agency considers that either can be utilized without distinction, given that the pharmacologically active molecule is glucosamine. However, some reports mention the possible interference with glucosamine sulfate absorption when administered in combination with CS.[17]

The safety profile of chondroitin and glucosamine is an important aspect. Among other advantages, they are safe in terms of cardiovascular health, as they do not increase the risk of myocardial infarction or stroke, even in patients with high cardiovascular risk,[18] in contrast to NSAID, especially in prolonged treatments, at high doses[19] and in combination with opiates.[20]

Finally, recent international guidelines have proposed that chondroitin and glucosamine, together with paracetamol, be the treatment of choice in osteoarthritis,[21] especially in patients with comorbidities taking multiple medications.

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