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CHONDROITIN SULFATE – CLINICAL REVIEW IN OSTEOARTHRITIS

Background:

Chondroitin sulfate (CS) belongs to the group of glycosaminoglycans, which are important structural constituents of cartilage extracellular matrix. In degenerative joint diseases, such as osteoarthritis, there is damage and loss of the articular cartilage. A key stage in the degenerative process is the loss of proteoglycan from the cartilage and the exposure of its collagen network to mechanical disruption[1].

Chondroitin sulfate (Condrosan® / Condrosulf®) is a symptomatic slow acting drug for osteoarthritis (SYSADOA) in Europe[2], where it has been approved as a drug for more than ten years in several countries.

Mechanisms of action:

The therapeutic activity of CS in osteoarthritis may be due to at least 4 main mechanisms which have been demonstrated up to now: 1) anti-inflammatory activity; 2) the metabolic effects on the synthesis of hyaluronate and on the cartilage proteoglycans; 3) the direct antidegradative actions which are realized by the inhibition of some proteolytic activities (collagenase, elastase, proteoglycanase,...) and by the decrease of dangerous effects on matrix molecules determined by reactive oxygen species; 4) inhibition of nitric oxide (inducer of cartilage destruction) in the joint[3,4].

Clinical evidence:

Up until now, 9 randomized clinical trials have been conducted in Europe with Condrosan® / Condrosulf®, comparing its effect against placebo (PBO) and sodium diclofenac (SD) (150 mg) in 1163 patients with knee and hand osteoarthritis[5-13].

The main outcome measures were Lequesne Index and Visual Analogue Scale (VAS). Secondary outcome measures were the assessments by patients and physicians, intake of rescue medication, etc

The results from these clinical trials conclude that CS is as effective as SD and around 50% more effective than PBO ($p < 0.05$) in the reduction of joint pain, functional disability, intake of rescue medication and global assessment of patients and physicians[5,14]. Thus, its efficacy as a SYSADOA is thoroughly confirmed

Another study, which evaluated the results of several clinical trials by means of the Emax model [methodology allowing to predict the maximal effect attainable (Emax) and the time required to reach 50% of Emax (T50) of any drug] shows that predicted maximal beneficial response in patients with knee OA receiving CS for 90 days is slightly greater than that predicted for SD. However, it takes twice longer for CS to achieve the maximal beneficial effect, whereas remnant effect of CS persists twice longer than that observed for SD[15].

There are also evidences that CS may act as a structure disease modifying osteoarthritis drug (S/DMOAD), that is, it may slow down disease progression[16]. Three clinical trials in patients with knee OA have evidenced a stabilization of joint space width with CS

treatment overtime as opposed to a narrowing of joint space in the PBO group[9-11]. On the other hand, two clinical trials in patients with hand OA concluded that disease progression was lower in CS-treated patients and less patients from this group developed erosive OA ($p< 0.05$)[12-13].

The tolerance of the product is very well documented. It is equivalent to that of placebo and much higher than that of SD[14]. Besides, pharmacosurveillance data from Europe, where no serious adverse events have been reported for more than 10 years, support the safety of the product.

Also, the fact that it is not metabolized by enzymes from cytochrome P450, entails that it can not present drug interactions at this level, which is extremely relevant for the elderly population, often overmedicated.

It is also noteworthy that CS has recently been classified by the European League Against Rheumatism (EULAR) under category 1A of maximum efficacy and safety. As for the effect size of the product, CS presents the highest effect range of all OA treatments, ranging from 1.23 to 1.50. (Clinically, an effect size of 0.2 is considered low; 0.5 moderate and 0.8 high)[16].

Bioequivalence:

There is only one CS with evidenced efficacy and safety and used in several clinical trials. Thus, it has been approved as a drug in Europe and is therefore considered as the reference product[17].

This CS is manufactured by Bioibérica (Spain) (CS® **Bio-Active)** and marketed in Europe by IBSA (Switzerland) and Bioibérica and in the the U.S.A. by Nutramax (under the trademark Cosamin®). Hence, this product should be considered as the reference formulation.

It is interesting to note that a study, which analyzed the contents of glucosamine and chondroitin sulfate of several products in the marketplace in the US, concluded that the amounts found of said substances were significantly different from the label claim in some products, with deviations from label claims ranging from as low as 0% to over 115. Furthermore, this same study also evidenced that characteristics such as: molecular weight, flexibility of structure, degree of sulfation and method of manufacture may influence oral absorption. Among all products compared, the one from Bioibérica evidenced the highest permeability rate[18]

Therefore, in order to ensure equivalent clinical results in terms of efficacy and safety, other CS products must show their bioequivalence to the reference formulation [17]

Note:

Bioibérica is the world leader in CS production, with factories in Spain, US (Nebraska) and China. Due to the high quality and clinical experience of our CS, it is being used by the National Institutes of Health (NIH) as the active ingredient for the Glucosamine / Chondroitin Arthritis Intervention Trial (GAIT)[19].

The corresponding Investigational New Drug Application number (IND) is 59,181. Also, BIOIBÉRICA submitted its Drug Master File of chondroitin sulfate to the FDA (registration number: 13.107) in August 1998.

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