REVIEW ARTICLE

Symptomatic slow-acting drugs (SYSADOAs)/disease modifying anti-osteoarthrosis drugs (DMOADs) in the treatment of osteoarthrosis: what is the opinion of the different rheumatology/osteoarthritis societies in 2021?

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Abstract
The various Rheumatology/Osteoarthritis Societies (the American College of Rheumatology, the Arthritis Foundation, the European League Against Rheumatism, the National Institute for Health and Care Excellence, the European society for clinical and economic aspects of osteoporosis and osteoarthritis, and the Italian consensus on appropriateness of osteoarthrosis therapies) published specific recommendations for the management of osteoarthrosis affecting hand, hip and knee. These evidence-based guidelines take into account safety and tolerability of pharmacological and non-pharmacological interventions available from the scientific literature as well as the opinions of the clinical specialists to provide complete, clear and transparent recommendations for the management of osteoarthrosis. This article provides an update of the scientific literature for selected treatments of osteoarthrosis focusing on the therapy with symptomatic slow-acting drugs (SYSADOAs) and disease modifying anti-osteoarthrosis drugs (DMOADs) (chondroitin sulfate, glucosamine, diacerein, unsaponifiable soy and avocado extracts). Moreover, the management of osteoarthrosis pain and function, avoidance of adverse events and long-term outcomes by SYSADOAs/DMOADs molecules is considered. Finally, based on the real-world data, the opinion of the various Rheumatology/Osteoarthritis Societies of all over the word is illustrated and discussed also by considering the structure, quality and properties of the SYSADOAs/DMOADs agents used in the treatment of osteoarthrosis. In particular, the results reported in numerous studies are contradictory and not always convincing about the efficacy of chondroitin sulfate and glucosamine as SYSADOAs and DMOADs. The cause of these non-homogeneous results could be due to the use in different studies of chondroitin sulfate and glucosamine preparations of varying quality. It is therefore mandatory to carry out new clinical studies using chondroitin sulfate and glucosamine of pharmaceutical grade or of the best possible quality to ascertain their usefulness as biomolecules in the treatment of osteoarthrosis.

Key Words: Osteoarthritis; SYSADOAs; DMOADs; Chondroitin sulfate; Glucosamine.

1. Introduction

Osteoarthritis (OA) is the most common joint disease and one of the main causes of reduced functionality and disability with significant costs related to the different treatments and high socio-economic burdens. Despite the recent results in knowledge on the pathogenesis of the disease, the treatment is still a challenge and contrary to inflammatory (autoimmune) joint diseases, there are currently no drugs available that can change the course and progression of OA. The different response in the different locations of the pathology further complicates the therapeutic choice. Standard drug treatment includes pain and inflammation control agents (non-steroidal anti-inflammatory drugs, analgesics including opioids, intra-articular corticosteroids) and the slow-acting symptomatic drug group (the SYSADOAs) for OA such as glucosamine hydrochloride. (GlcNH)/glucosamine sulfate (GlcNS), chondroitin sulfate (CS), diacerein, unsaponifiable soy extract and avocado extract, administered orally, and intra-articular hyaluronic acid (HA). In addition, several studies are evaluating the efficacy of SYSADOAs used in the inflammatory arthritis mentioned above as potential therapies (the so-called DMOADs) capable of slowing down and/or reversing the progression of structural changes in cartilage caused by OA.

Slow-acting agents used to treat OA are divided into two classes, such as **Sy**mptomatic **S**low-**A**cting **D**rugs for **OA** (SYSADOAs) and those capable of modifying the progression of OA disease (**D**isease **M**odifying anti-**OA D**rugs, DMOADs).[1-3] SYSADOAs, including CS, GlcNH and GlcNS, do not possess analgesic abilities and their effects arise only after administration for medium to long periods, generally after prolonged treatment for 2-3 weeks. Their effects are symptomatic of pain relief and continue for a long time even after the end of therapy (usually a couple of months) as opposed to non-steroidal drugs (NSAIDs) which require continuous administration to obtain analgesic effects.[4] DMOADs, on the other hand, are agents capable of preventing, delaying progression or even reversing morphological changes with effects on the joint structure.[5] DMOADs inhibit the progression of structural changes caused by the disease and thus improve symptomatology and/or function.

2. Chondroitin sulfate

CS belongs to the class of natural complex polysaccharides called glycosaminoglycans (GAGs). It is a biological macromolecule with a complex structure, unbranched, polydisperse, extracted and purified from various animal tissues and organs.[2,6-8] CS is composed of variously sulfated disaccharide sequences formed by monosaccharide residues of D-glucuronic acid (GlcA) and N-acetyl-D-galactosamine (GalNAc). Several types of CS are known having different carbon skeletons which differ in the nature of the disaccharides involved. For example, CS-4-sulfate, or CSA, is made up of sulfated disaccharides in position 4 of GalNAc, while CS-6-sulfate, or CSC, is mainly composed of sulfated disaccharide units in position 6 of GalNAc (Figure 1A). However, although the known CS samples are mainly composed of various percentages of these two types of disaccharide units, disaccharides with a different number of sulfate groups bound in different positions may be present, in various percentages, within the polysaccharide chains (Figure 1A). The heterogeneity in the number of sulfate groups linked to the polysaccharide chain of

the CS is responsible for the great variability in the charge density as well as for the presence of low or high sulfated sequences. Furthermore, the number of disaccharide units that form the polymer is another key factor that influences the biological and pharmacological activity of CS. Consequently, CS represents a widely heterogeneous family of polysaccharides in terms of degree of sulfation, localization of sulfate groups and molecular weight depending on the tissue of origin.[2,6-8]

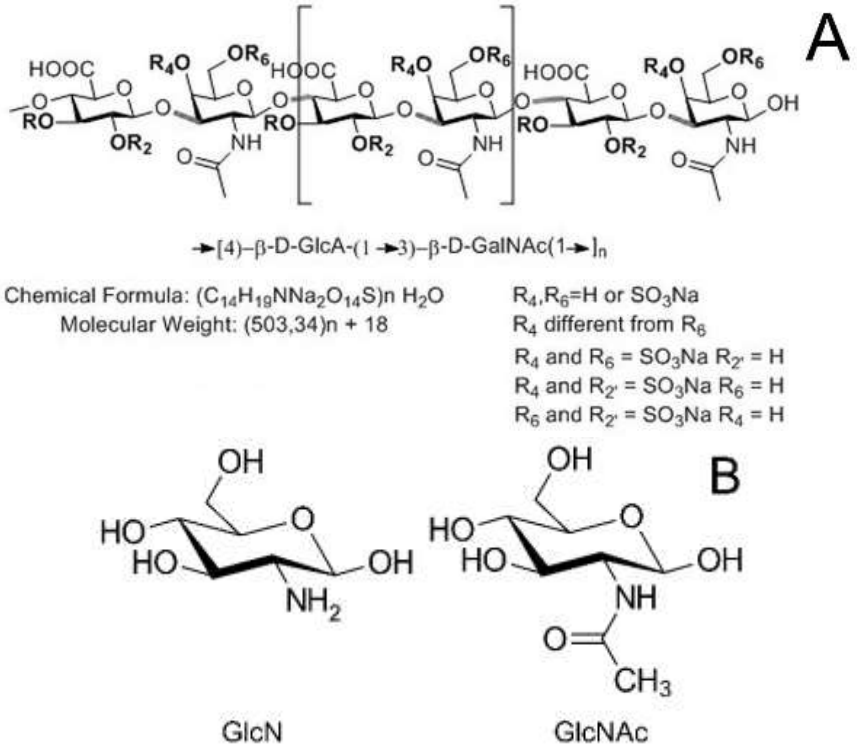

Figure 1 A) Chemical structure of chondroitin sulfate. The main positions in which the sulfate groups can be esterified are also reported. **B)** Chemical structure of glucosamine (GlcN) and N-acetyl-glucosamine (GlcNAc).

For commercial applications, CS must be produced from organs and tissues, in particular from cartilages of terrestrial (bovine, pig, chicken) or marine (mainly from cartilaginous fishes) animals[6-8] and depending on the various animal sources, CS possessing different structure and biological properties can be obtained. Moreover, several important structural modifications of the CS backbone can be introduced by the different extractive procedures applied by the various factories, in particular desulfation, depolymerization and/or chemical alterations. As a consequence, CS for industrial, nutraceutical and pharmaceutical applications can vary for structure, physicochemical properties, title and purity as well as for biological activity, bioavailability and pharmacokinetic.[9]

As mentioned, CS possesses various negative charges thanks to the presence of GlcA and the different sulfate groups with which it is able to interact with numerous

proteins and cellular biomolecules and the extracellular matrix and therefore to regulate their activity.[10] CS is considered to be the most widely used SYSADOA for the treatment of OA.[11] The main reasons are 1) the ability of CS to slow down the development of OA demonstrated in several clinical studies with significant positive effects including the possibility to decrease the dosage of other treatments such as NSAIDs, better gastrointestinal tolerability by limiting the risk of ulcers of the gastrointestinal tract and deleterious effects on the renal system of elderly patients; 2) the effect of CS in patients with OA is hypothesized to be due to its anti-inflammatory activity,[3, 12] to the stimulation of the synthesis of proteoglycans and HA and to the decrease the catabolic activity of chondrocytes by inhibiting the synthesis of proteolytic enzymes, nitric oxide and others mediators that help damage the cartilage matrix and cause cell death[3,11]; 3) in most cases, CS shows a residual effect that lasts further months after the end of treatment, a feature that is never seen with analgesics and NSAIDs, substances that must be continuously administered to provide pain relief and increased autonomy in patients with OA; 4) some studies have shown that CS plays a role in the formation of new bones, cartilages and tendons, as a DMOAD agent, and also helps to maintain the structural integrity of the tissues; 5) CS is involved in specific biological functions, such as cell adhesion and division, morphogenesis, formation of neural networks.[10]

The main factor causing inflammation in OA is the activation of the nuclear factor-κB (NF-κB). The CS is able to reduce the activation of this factor and its nuclear translocation in chondrocytes and in the synovial membrane.[3,11,12] In general, in OA, two types of patterns are observed in processes involving inflammation: the first is the molecular pattern associated with damage, the so-called DAMP,[11] while the second is the molecular model associated with pathogens, the PAMP, which includes bacteria, viruses and fungi. DAMPs stimulate the immune system, via specific receptors, to fight infection or initiate the repair process, inducing innate immunity or the host's immune response. Following joint trauma or overstressing, tissue associated molecular damage (DAMP), such as damage related to the extracellular matrix (ECM) of cartilage including fibronectin, HA and intracellular alarmins, signal to specific receptors on synovial macrophages, fibroblast-like synoviocytes (FLS) and chondrocytes the need to induce local production of inflammatory mediators that induce further chondrolysis and release of additional ECM degradation products such as Tenascin C and HA fragments. The different mediators generated induce the production of pro-inflammatory cytokines including tumor necrosis factor (TNF-α) and interleukin-1β (IL-1β) as well as matrix metalloproteinases (MMP1 and MMP3). In addition, the angiogenesis induced by inflammation and greater vascular permeability cause the subsequent influx of plasma proteins, further increasing the DAMP. The acute and chronic production of inflammatory mediators directly or indirectly promotes the further degradation of cartilage through the induction of proteolytic enzymes, amplifying the activation of the immune system in a vicious circle. Neutrophils and monocytes pass through endothelial cells causing edema (and swelling). Mast cells and macrophages, by releasing histamine, leukotrienes and prostaglandins, increase vascular permeability. Neutrophils create a cytotoxic environment by degranulation,

releasing highly reactive toxic chemicals such as oxygen and nitrogen free radicals (ROS and RNS, respectively) and various proteolytic enzymes (Figure 2). The collective effects of all these molecular phenomena produce heat, swelling, redness, pain and loss of function.

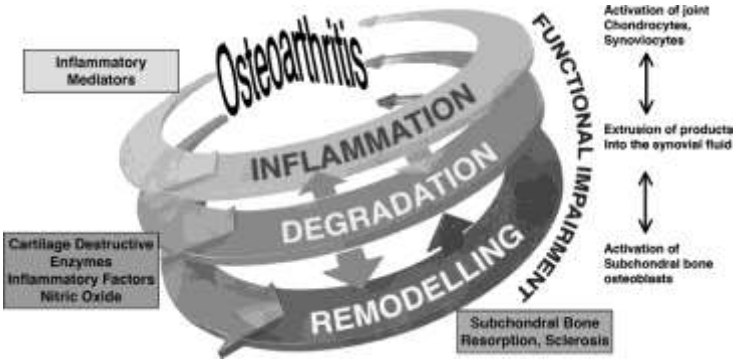

Figure 2. Schematic and general representation of chronic inflammation in osteoarthritis (Reproduced with permission from Volpi N, Condrosulf®: structural characterization, pharmacological activities and mechanism of action, Curr Med Chem 2014;21:3949-3961).

CS expresses its therapeutic efficacy through the involvement of various receptors, directly and/or indirectly modulating the anti-inflammatory effects. As mentioned, CS is a large macromolecule and therefore cannot penetrate inside the chondrocytes. For this reason, oligosaccharides and CS sequences interact with membrane receptors, such as CD44, RHAMM and intercellular adhesion molecule 1 (ICAM1), promoting the activation of molecular cascades that reduce the nuclear translocation of NF-κB and thus the inflammatory process (Figure 3). Furthermore, CS activates integrins and increases the expression of transforming growth factor-1β (TGF-1β) which favors the synthesis of high molecular weight HA and collagen II.[3,11] Finally, CS acts directly by decreasing the presence of different complement components and indirectly by lowering metallo-proteinases (MMP1 and MMP3) as well as demonstrating anti-angiogenic action (Figure 3).

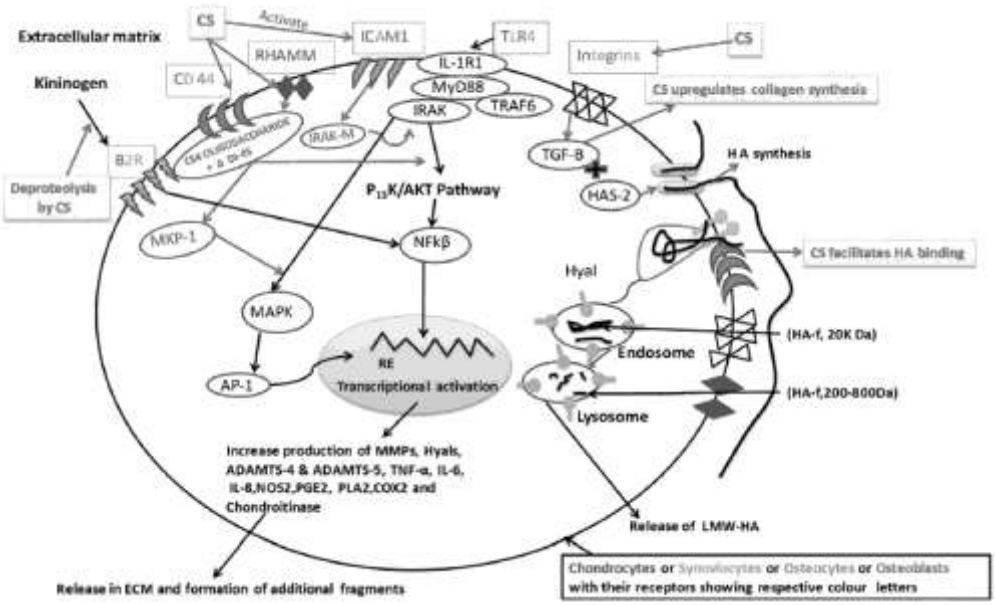

Figure 3. Specific metabolic pathways in which chondroitin sulfate can intervene by exerting its anti-inflammatory activity (Modified by Bishnoi M *et al.*[11]).

From what has been said, CS also stimulates the anabolic processes of the cartilage by increasing the synthesis of HA, proteoglycans and collagen II thus behaving as a DMOAD. In its anti-inflammatory action, CS reduces pro-inflammatory factors and proteases by improving the anabolic/catabolic balance of the ECM, also reducing the loss of cartilage volume, slowing the loss of joint space and consequently decreasing pain. CS can affect the processes associated with cartilage degeneration also by inducing the production of proteoglycans by biosynthetic enzymes, inhibiting the activity of elastase and cathepsin G, and reducing the gene expression of a series of proteolytic enzymes.[3,11]

3. Glucosamine

GlcN is an amino sugar, constituent of numerous important macromolecules present in the ECM of mammals, in articular cartilage, synovial fluid, exoskeletons of crustaceans, arthropods, as well as the cell wall of fungi. Indeed, GlcN is used for the synthesis of GAGs, proteoglycans, glycolipids and glycoproteins and is the biochemical precursor of all amino sugars.[1,13] The chemical structure of GlcN is 2-amino-2-deoxy-α-D-glucose (Figure 1B), similar to glucose with an NH_3 amino group in position C2 (molecular formula $C_6H_{13}NO_5$). GlcN is naturally biosynthesized from fructose-6-phosphate and glutamine by glutamine: fructose-6-phosphate aminotransferase which is further acetylated to N-acetyl-glucosamine (GlcNAc) by glucosamine N-acetyl transferase which is then used for the synthesis of glycoproteins, glycolipids and GAGs.

As previously anticipated, there are three different forms of GlcN on the market: glucosamine hydrochloride (GlcNH), glucosamine sulfate (GlcNS) and N-acetyl-glucosamine (GlcNAc). These compounds are usually prepared from chitin through various methods including the chemical or enzymatic hydrolysis of the chitin itself and

the production by microbial fermentation.[3,13] Recently it has been possible to produce these amino sugars by fermentation of genetically modified fungi or bacteria, in particular *Escherichia coli*.[3]

As for CS, the most described mechanism for understanding the anti-inflammatory effects of GlcN is the inhibition of the activation of the molecular cascade activated by NF-κB through the repression of the nuclear translocation of p65 and p50. Consequently, this transcription factor cannot translocate to the nucleus and activate the transcription of genes involved in inflammatory responses, such as the TNF-α and INF-γ[13] mediators. Reduction of these mediators blocks ICAM-1 gene expression (intercellular adhesion molecule or CD54) and protein synthesis. ICAM-1 binds to a specific receptor on leukocytes forming a complex critical for the activation and migration of T cells. This complex acts as a co-stimulatory signal for the activation of T lymphocytes. Therefore, the decrease of ICAM-1 causes suppression of T lymphocytes. Furthermore, GlcN directly inhibits IL-1 b-induced activation of NF-κB and also prevents cytokine-induced demethylation of a specific CpG site in the IL-1 promoter thereby decreasing the expression of IL-1b.

The cyclooxygenase-2 (COX-2) and matrix metalloproteinase (MMP) families play an important role in inflammatory processes due to prostaglandin production and degradation of the extracellular matrix, respectively. Inhibition of these enzymes therefore appears to be an effective way to improve the symptoms and progression of inflammatory diseases. GlcNS has been shown to alleviate OA symptoms by regulating the synthesis of MMP family members and IL-1-induced COX-2 gene expression, decreasing prostaglandin E2 synthesis, increasing HA production, and of cartilage matrix protein in human synovial explants. Furthermore, GlcN is able to modify the protein profile in human articular chondrocytes with an increase in specific proteins involved in the anti-inflammatory process such as GRP78 (an anti-apoptotic chaperone) and/or a decrease in proteins related to the oxidative response to stress such as SOD2 (mitochondrial superoxide dismutase). The GRP78 protein promotes the secretion of anti-inflammatory cytokines including IL-10, IL-1Ra and the soluble factor TNFR from monocytes.

More recently, however, some studies have suggested that GlcN functions more as an immunomodulator rather than as an immunosuppressant *in vivo*.[13] Systemic administration of GlcN can regulate the production of the cytokines Th2, IL-5 and IL-10, which suppress the Th1 response in an experimental autoimmune encephalomyelitis model, leading to minimizing the proliferation of T cells with cytolytic activity.

Several studies have also demonstrated the antioxidant activity, a strong chelating effect on ferrous ions and GlcN ability to remove free radicals.[13] Oral administration of GlcN during murine pulmonary inflammation processes is able to directly inhibit the activity of NADPH oxidase followed by a decrease in the production of reactive oxygen species (ROS) and prevention of translocation of $P47^{phox}$ from the cytoplasm to the membrane that it is crucial for the activation of NADPH oxidase. Other results have shown that GlcN can protect macromolecules such as proteins, lipids and DNA from oxidative damage induced by hydroxyl radicals as well as it has been shown that GlcNS can protect proteins from oxidation and improve the reduced

glutathione level in oxidatively stressed human chondrocytes. Finally, GlcN could be a suitable agent for the prevention of DNA damage induced by H_2O_2 in human peripheral lymphocytes, thanks to the presence of the free amine of the NH_2 group with positive charge present in the molecule. All these results suggest that this amino sugar has antioxidant and cytoprotective properties and therefore can be considered a promising agent in the prevention and/or treatment of ROS-related diseases.

Thanks to its effects at the molecular and cellular level, long-term administration of GlcN can slow down changes in the joint structure, suggesting a potential benefit beyond symptom and pain control when used early in the management of OA, thus acting as a DMOAD agent.[14]

4. Chondroitin sulfate and glucosamine in the treatment of osteoarthritis

CS is administered exclusively orally while GlcN is administered primarily orally and rarely intravenously or topically. CS is administered with a dosage greater than 800 mg/day (generally 1,200 mg/day) while GlcN at a dose greater than or equal to 1,500 mg/day, according to the dosage granted in Europe.[15,16]

Several meta-analysis studies have been performed and available to evaluate the efficacy and safety of GlcN and CS (SYSADOA agents) administered individually or in combination on the treatment of knee and/or hip OA. In a recent meta-analysis work,[16] twenty-six scientific articles were evaluated that report the results of 30 randomized studies selected on the basis of their high methodological quality. The overall results of this meta-analysis demonstrate that CS can relieve pain symptoms and improve function compared to placebo in patients with OA while GlcN has a significant effect only on the ability to improve joint stiffness. In contrast, oral administration of CS and GlcN in combination showed no effects superior to placebo with no significant difference in the incidence of adverse events,[14,16] also in agreement with other studies.[17] However, in a subgroup of patients with moderate to severe knee pain, there was significant relief of joint pain following combination therapy with CS and GlcN.[17]

In another recent meta-analysis study,[18] combining seven clinical trials with GlcN and eight with CS, both were shown to be highly effective compared to placebo in improving all parameters considered in patients with OA. Furthermore, in agreement with the previous study,[16] CS has been shown to be effective in reducing pain-related symptoms.

A further meta-analysis suggested a mild to moderate efficacy of CS in the symptomatic treatment of OA, with an excellent safety profile.[19]

In 2005-2006, the National Institute of Health (NIH) sponsored a study known as GAIT to test the effects of CS and GlcN, administered separately or in combination, on patients with knee OA.[20] GAIT was the first large-scale multicenter study in the United States, coordinated by the University of Utah, School of Medicine, conducted by 16 research centers in rheumatology, with the aim of testing the short-term (6 months) ability to CS and GlcN in reducing pain in 1,583 recruited patients, aged 40 years or older. Five treatment groups were evaluated: CS alone (400 mg 3 times per day), GlcN alone (500 mg 3 times per day), CS and GlcN in combination (1,200 mg plus 1,500 mg per day), celecoxib (200 mg per

day), or placebo. The results of the GAIT study showed that, in a subset of patients with moderate to severe pain, the combination of CS and GlcN provided statistically significant pain relief compared to placebo. Conversely, in patients with mild pain, CS and GlcN alone or in combination did not show significant effects.[20]

In 2008 another GAIT study was performed to evaluate the effect of possible structural modifications of the knee (DMOAD effect) in subjects with OA. Although the differences were not statistically significant, treatment with CS and GlcN showed improvement in patients with Kellgren/Lawrence grade 2 OA.[21]

5. Other possible chondroprotectors and nutraceuticals used in the treatment of osteoarthritis

5.1. Boswellia serrata.

The gummy resin extracted from Boswellia serrata is a powerful anti-inflammatory with few side effects. The most active component of Boswellia extract is 3-*O*-Acetyl-11-keto-beta-boswellic acid (AKBA) capable of inhibiting 5-lipoxygenase (5-LOX) and the complement system involved in the cascade inflammatory at the cellular level.[22] Boswellia extract also reduces the production of pro-inflammatory cytokines, the expression and activation of MMP-9 and MMP-13 and also the production of nitrites, prostaglandin E2 and cyclooxygenase-2. In a four-week study,[23] pain, joint stiffness and physical function according to the WOMAC scale were found to be significantly improved in the Boswellia group compared to controls. These findings were confirmed in a subsequent 12-week follow-up study.[24] In additional 90-day, randomized, double-blind, placebo-controlled studies, Boswellia extracts were shown to be significantly effective in improving pain and physical condition in patients with knee OA.[22]

5.2. Curcumin.

The root and rhizome of the Curcuma longa plant provides the extract in which curcumin is the main constituent (77%) although it contains other important components such as bis-demethoxy-curcumin (17%). Curcumin inhibits the production of IL-1beta and TNF-alpha by acting as an anti-inflammatory agent.[22] It was observed that curcumin was effective in improving all clinical parameters according to the WOMAC scale in patients with knee OA, results confirmed by a subsequent multicenter study.[22]

5.3. Diacerein.

The mechanism of action of diacerein, an anthraquinone, is not fully known, although *in vitro* it inhibits phagocytosis and macrophage migration, inhibits the production of interleukin-1 and causes a reduction in the activity of some proteolytic and collagenolytic enzymes which act on the proteoglycans of the arthritic cartilage.[25] It is also considered an active molecule such as SYSADOA with anti-inflammatory, antioxidant and anti-apoptosis activity.[25] Five clinical trials have been conducted by administering diacerein to patients with OA of the hip and/or knee.[12] However, the results of these studies were heterogeneous and not definitive. In addition, in two studies carried out to evaluate the ability of diacerein to modify joint structures, they gave opposite results with a significant improvement in the cartilage structure of the hip, which was however negative in subjects suffering from knee OA. Finally,

both studies identified diarrhea as a significant side effect.

5.4.Unsaponifiable extract of avocado and soy (ASU).

This product is a plant extract made from avocado fruits and seeds and soybean oil. ASU is a complex mixture of many molecules, including fat-soluble vitamins, sterols, triterpene alcohols, and possibly furan fatty acids. However, the identity of the active component(s) is still unknown. The ASU has been shown to possess chondroprotective, anabolic and anti-catabolic properties.[16] In clinical studies, slight improvement in pain and joint stiffness was observed following administration of ASU for short periods at a dose of 300 mg/day.[16] However, conflicting results have been obtained on disease progression in 2-3 year studies in the treatment of patients with hip or knee OA.[16] In a systematic review of clinical trials of hip/knee OA treatment, it was concluded that ASU is effective in relieving pain and improving joint function, with a better effect in hip than in knee, without however presenting significant quantitative data.[26]

6. Opinions of the various rheumatology/ osteoarthritis societies

CS is widely used, especially in the USA, as a "food supplement" and nutraceutical where it is also authorized, while in Europe and in some other countries it is used as SYSADOA with the limits and recommendations dictated by the various Rheumatology/Osteoarthritis Societies. GlcN is also widely sold as a nutraceutical alone or in combination with CS or other active ingredients, while GlcNS is recommended by the Rheumatology/Osteoarthritis Society in a proprietary form known as crystalline (pCGS).[27]

In 2019, the American College of Rheumatology (ACR) and the Arthritis Foundation (AF) developed specific recommendations for the management of OA affecting hand, hip and knee.[28] These evidence-based guidelines take into account safety and tolerability of pharmacological and non-pharmacological interventions available from the scientific literature as well as the opinions of the clinical specialists to provide complete, clear and transparent recommendations for the management of OA.[28] Based on this methodology, ACR/AF discourages the single use of CS as well as in combination with GlcN for the treatment of patients affected by knee and/or hip OA. However, CS is conditionally approved for the administration in patients affected by hand OA (Figure 4) based on a single clinical trial showing its analgesic efficacy.[28] Based on the same approach, GlcN is strongly advices against in patients with OA affecting all cartilages (knee, hip and hand). In fact, several discrepancies in efficacy were found between industry sponsored and publicly funded studies. Furthermore, there is a clear lack of biological understanding linked to varying efficacy with the type of GlcN salt studied. The data available in the scientific literature show no important advantages in using any form of GlcN compared to placebo. However, GlcN remains among the most commonly used dietary supplements in the United States,[29] and clinicians should be aware that many patients perceive GlcN as effective as well as combining its different forms with differing efficacy. The potential toxicity of GlcN regardless of its chemical forms is low, although some patients have shown increases in plasma glucose levels.[30]

Finally, the ACR/AF points out that at present, no DMOAD agents are available for therapeutic use, although phase 2 and 3 clinical trials are underway for several possible candidates.

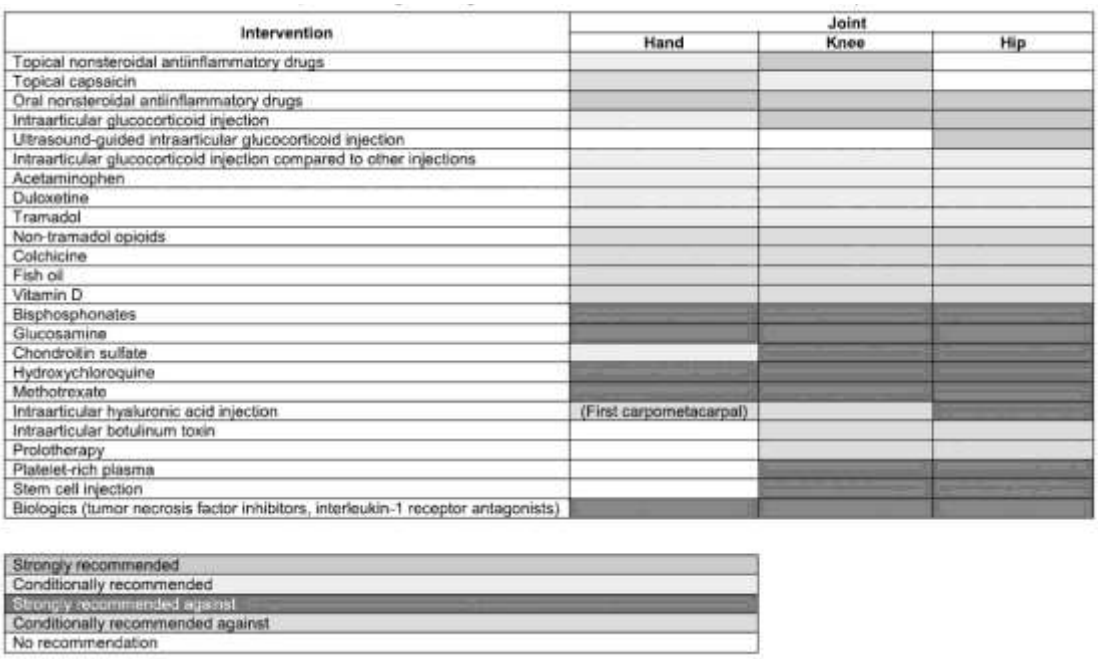

Figure 4. Recommendations of the ACR/AF for the pharmacological management of osteoarthritis of the hand, knee and hip (Reproduced with permission from Kolasinski SL *et al.*[28]).

Since the last publication in 2007 by the European League Against Rheumatism (EULAR) for the management of OA of the hand,[31] new data and clinical studies have been published in a recent article from 2018.[32] Applying standardized operating procedures from EULAR, a systematic review of the scientific literature has been carried out, collecting data on non-pharmacological, pharmacological and surgical treatment options for hand OA. General principles and recommendations were formulated based on clinical data updated to 2018 and expert opinions from an international task force consisting of 19 doctors, healthcare professionals and patients from 10 European countries. Based on the recommendations published in the latest literature review by EULAR, CS can be used in patients with hand OA to relieve pain and improve joint function. In fact, CS has been shown to be effective in relieving the symptoms of OA in the hand, although no clinically significant effects have been found in patients with OA of the knee and hip. The EULAR also confirms the results published by the ACR/AF described above[28] regarding the data obtained by administering GlcN in patients suffering from OA of the knee, hip and hand in which no improvement effects were found compared to placebo. Due to the limited evidence and even less convincing data available to support the use of CS and/or GlcN in the treatment of knee and hip OA (and hand for GlcN), EULAR discourages the use of these agents in treatment of the aforementioned diseases.

Following extensive and extensive evaluations of all available clinical studies

on the use of CS and GlcN in the treatment of OA of the knee, hip and hand, important guidelines were published in 2014 by the NICE (National Institute for Health and Care Excellence, UK).[33] The working group considered pain, function, any structural changes and possible adverse events as critical parameters for decision making. Other decision-making criteria were joint stiffness, the OMERACT-OARSI response index and the patient's overall assessment. CS showed a possible benefit over placebo in reducing pain measured by a visual analogue scale (VAS) in both short- and long-term treatments, although there was uncertainty regarding these effects and the quality of clinical trials performed. In short-term treatments (less than 13 weeks) CS produces ameliorative effects compared to placebo. Furthermore, some studies of moderate methodological quality and longer than 13 weeks in duration suggest that CS may be more effective than placebo in protecting cartilages from joint space reduction. The working group also determined that all GlcN preparations compared to placebo showed no clinically important differences in pain. In conclusion, after carrying out a thorough clinical review, separating high and low quality studies, the working group decided that the overall evidence on the efficacy of CS and all the different chemical forms of GlcN remained very limited and uncertain.[33]

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) published in 2014 and updated in 2016[34] an algorithm (Figure 5) for the treatment and management of knee OA that provides further evidence to support pharmacological interventions. Studies using pharmaceutical grade CS have demonstrated its clinical efficacy on joint structure changes in patients with mildly moderate OA and that the effect on pain is variable. It is the opinion of ESCEO that although, as mentioned, numerous formulations of GlcN are available in the form of generics, over-the-counter products and dietary supplements, only the patented crystalline GlcN (pCGS) has shown superior efficacy in the treatment of OA compared to placebo in the treatment of pain and functional skills.[30] In conclusion, the preferential approach to the treatment of knee OA recommended by the ESCEO is to start therapy with SYSADOAs, with the addition of paracetamol as needed (Figure 5). Among the SYSADOAs, the pharmaceutical grade CS and the pCGS show greater efficacy as evidenced by several clinical studies and by the review of the same by the ESCEO.[34,35]

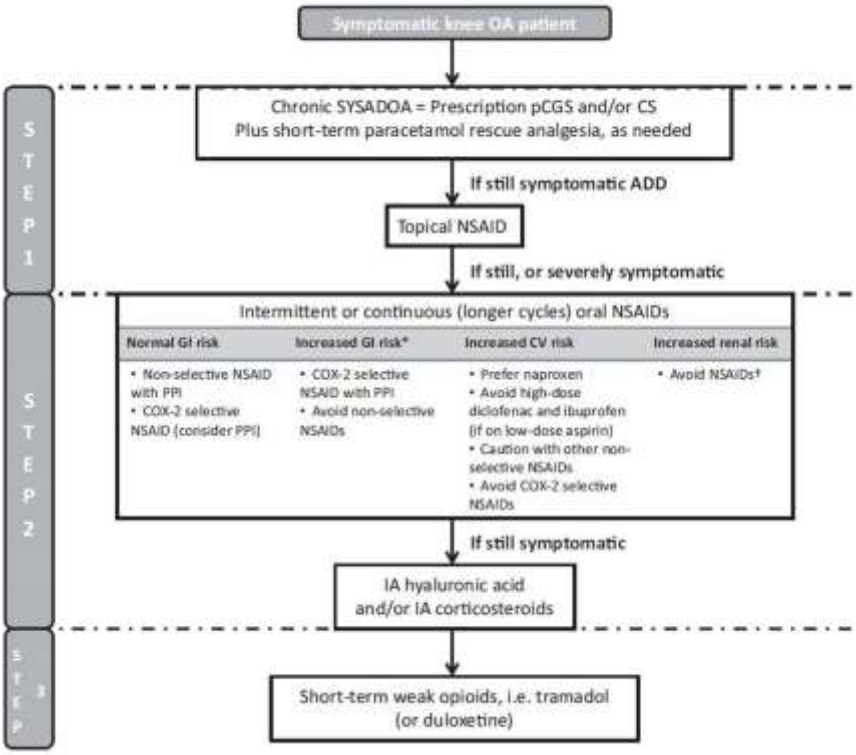

Figure 5. Algorithm defined by ESCEO for the pharmacological management of knee osteoarthritis. *Including the use of low-dose aspirin; †With glomerular filtration rate <30 cc/min; COX-2, cyclooxygenase-2; CS, chondroitin sulfate; CV, cardiovascular; GI, gastrointestinal; IA, intra-articular; NSAIDs, non-steroidal anti-inflammatory drugs; pCGS, patented crystalline glucosamine sulfate; PPI, proton pump inhibitor (Reproduced with permission from Bruyère O et *al*.[34]).

In 2019, a committee of eleven experts was set up between Italian universities, public hospitals, local services, research institutes and patient associations to define some guidelines for the treatment of OA, use of drugs and medical devices and their effectiveness.[36] The committee essentially transposed the indications of the ESCEO indicating the SYSADOAs useful in the treatment of OA. However, according to the ESCEO, it is emphasized that only pCGS and pharmaceutical grade CS are considered effective in the first-line treatment of knee OA as an alternative drug to paracetamol. Furthermore, it is reported that some guidelines for OA do not agree in recommending the use of SYSADOA perhaps because they are generally considered as a single class of molecules in addition to not making distinctions between the different formulations available.

Regarding other possible agents SYSADOA and/or DMOAD (such as Boswella and curcumin extracts, ASU and diacerein), ACR, EULAR and NICE do not consider them therapeutic agents useful for the treatment of OA on weak or completely absent clinical evidence base. To confirm this negative opinion, ESCEO recommends the use of SYSADOA formulations with proven efficacy and safety data for current clinical practice.[35]

7. Conclusions

OA is expected to become an ever-increasing burden in the coming decades.

The first recommendations of the main guidelines for avoiding or limiting the progression of OA invite patients to change their lifestyle, lose weight and practice physical exercise.[33] Secondly, drug treatments may be needed, and new compounds have been developed to combat the degenerative progression of joint disease. To this aim, we should also consider that the most important side effects are related to the prolonged and probably dose-dependent[37] use of NSAIDs producing increased cardiovascular or gastrointestinal diseases. Moreover, the research of new compounds able to reduce the progression of OA and improve the quality of the life of patients with no or limited side-effects is expensive and time-consuming with possible future risks and uncertain markets.[38] Moreover, by also considering that the choice of a new active molecule depends on several other aspects such as cost-benefit ratio and each National Institute of health rules, the development of new drugs useful for the treatment of OA is a challenge of the future.

CS and GlcN (and their derivative products) are widely used as drugs or nutraceutical/food supplements in the therapy of OA and the aging of the population and the relative increase of this pathology has further increased the demand for these active ingredients. CS is prescribed or used as an over-the-counter drug in 22 countries and is regulated as SYSADOA in Europe. In the United States, it is indicated as a dietary supplement and therefore analytical standards are not mandatory for the preparation of the formulations while in Europe it is approved as a drug or reference product requiring approval of efficacy and safety. GlcN is available by prescription as a proprietary crystalline GlcNS (pCGS), as a generic and over-the-counter (OTC) formulations, and as a dietary supplement containing primarily GlcNH. The different generics of GlcN, over-the-counter medications, food/nutritional products and supplements vary substantially in their different molecular forms, pharmaceutical formulations, and dosage regimens. However, despite the wide use and presence on the market of different CS and/or GlcN-based products for the treatment of OA, there is no unambiguous consensus among the different International Societies of OA and rheumatology and their use is highly questionable (Table 1). The main source of disagreement on the use of SYSADOA stems from the fact that the regulatory status and, consequently, the availability and labeling of these active ingredients differ substantially between countries and regions of the world. Added to this is the high structural heterogeneity and quality of CS and the different molecular forms and qualities of GlcN. At the moment, according to the ACR/AF and the EULAR, CS is conditionally recommended for patients suffering from OA of the hand while GlcN is strongly discouraged. Partially confirming the recommendations of the ACR/AF and EULAR, NICE expresses doubts about the effectiveness of CS and all the different chemical forms of GlcN. The ESCEO and the committee of Italian experts have a different opinion, agreeing on the clinical efficacy of pharmaceutical grade CS and patented crystalline GlcN (pCGS) (Table 1).

Table 1. Last opinion of the different rheumatology/osteoarthritis societies.

	Chondroitin sulfate	**Glucosamine**	**Chondroitin sulfate + Glucosamine**	**Boswellia serrata, Curcumin, Diacerein, Unsaponifiable extract of avocado and soy (ASU)**
American College of Rheumatology (ACR)	Approved only for the treatment of hand OA	Not Approved	Not approved	Not approved
Arthritis Foundation (AF)	Approved only for the treatment of hand OA	Not Approved	Not approved	Not approved
European League Against Rheumatism (EULAR)	Approved only for the treatment of hand OA	Not Approved	Not approved	Not approved
National Institute for Health and Care Excellence (NICE)	CS produces ameliorative effects compared to placebo	The efficacy of all the different chemical forms of GlcN remains very limited and uncertain	Not reported	Not approved
European society for clinical and economic aspects of osteoporosis and osteoarthritis (ESCEO)	Approved only CS of pharmaceutical grade	Approved only the patented crystalline glucosamine sulfate	Not reported	Not reported
Italian consensus on appropriateness of osteoarthrosis therapies	Approved only CS of pharmaceutical grade	Approved only the patented crystalline glucosamine sulfate	Not reported	Not reported

If the different molecular forms, pharmaceutical formulations and dosage regimens of GlcN available for the treatment of OA can cause conflicting clinical efficacy, the structural complexity of CS certainly plays a key role in its therapeutic capacity. As previously discussed, along with its intrinsic complex macromolecular structure, the biomolecule CS must be purified from animal tissues with all the problems related to the heterogeneity of the extractive sources and the reproducibility of production processes.[2,6,7] Consequently, due to this structural and quality variability of the products used in therapeutic or nutraceutical applications, CS may have different biological and clinical activities.

In conclusion, the results on the efficacy of CS and GlcN as SYSADOAs and DMOADs reported in numerous randomized clinical trials and meta-analysis studies are contradictory and not always convincing. At the moment, therefore, it is not possible to have absolute certainty about their effectiveness in modifying the course of the disease and their use in the treatment of OA is discordant. The cause of these non-homogeneous results could be due to the use in different studies of CS and GlcN

preparations of varying quality. It is therefore necessary to carry out new accurate clinical studies using pharmaceutical grade CS and GlcN of the best possible quality to ascertain their usefulness as bioactive molecules in the treatment of OA.

Abbreviations

ACR, American College of Rheumatology. AF, Arthritis Foundation. CS, chondroitin sulfate. DMOADs, disease modifying anti-OA drugs. ECM, extracellular matrix. ESCEO, European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis. EULAR, European League Against Rheumatism. NSAIDs, Non Steroidal Anti-Inflammatory Drugs. GAGs, glycosaminoglycans. GalNAc, N-acetyl-D-galactosamine. GlcA, D-glucuronic acid. GlcNH, glucosamine hydrochloride. GlcNS, glucosamine sulfate. GlcNAc, N-acetyl glucosamine. HA, hyaluronic acid. NF-κB, nuclear factor-κB. NICE, National Institute for Health and Care Excellence. NIH, National Institute of Health. OA, osteoarthritis. pCGS, crystalline glucosamine sulfate. SYSADOAs, symptomatic slow-acting drugs for OA.

Declarations

1. Ethics approval and consent to participate: not applicable.
2. Consent to publish: the Author received all authorizations to publish the reported material.
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