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Editorial

Importance of pharmaceutical composition and evidence from clinical trials and pharmacological studies in determining effectiveness of chondroitin sulphate and other glycosaminoglycans: a critique

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Abstract

Objectives Chondroitin sulphate (CS) has attracted much interest over the past two decades or so as a biological agent for use in the relief of pain and joint symptoms in osteoarthritis. Earlier clinical investigations produced variable, if encouraging results. This variability was partly due to limitations on the study designs and the lack of availability of standardized CS. Recently, high quality and fully standardized CS (Condrosulf) has become available and its effects have been studied in large-scale osteoarthritis trials, which are discussed here.

Key findings There is now evidence for symptom- and structure-modifying (radiologically-observed) effects. These studies show that CS (a) has slow onset of response and that relief of pain may not be like that of the direct analgesic actions of non-steroidal anti-inflammatory drugs (NSAIDs), (b) there are indications of reduced need for intake of analgesics (e.g. NSAIDs) in patients taking CS, and (c) quality of life and cost-benefits may be associated with use of CS. Safety evaluations show that the incidence of adverse reactions is low. Pharmacokinetic studies indicate that although oral absorption is relatively fast CS has moderate oral bioavailability (15–24%) and that depolymerised and degraded CS that is evident after absorption, together with CS itself, may take some time to accumulate in target joints. The pharmacodynamic actions of CS indicate that it has anti-inflammatory effects that include multiple actions involving reduction of catabolic reactions and enhanced anabolic (proteoglycan) synthetic reactions in cartilage and may block osteoclast activation in bone. Further studies are required to (a) establish the effects of depolymerised and degraded CS on degradation of cartilage and bone *in vitro*, and (b) MRI and other investigations of the effects in osteoarthritis of long-term CS treatment.

Summary The findings from this review show there may be potential value of CS in reducing the dependence on intake of NSAIDs and analgesics in patients with osteoarthritis, while at the same time having favourable safety.

Keywords arthritis; chondroitin sulphate; glycosaminoglycans; inflammation; pharmaceutical analysis

A glance at the shelves in pharmacies and natural products counters of stores and supermarkets in North America, Europe, South East Asia and Australia reveals an extraordinary array of products containing chondroitin sulphate (CS), glucosamine (hydrochloride (GH) or sulphate (GS)), methyl sulphonyl methane and mussel extracts, which are sold for the relief of pain and symptoms of arthritic diseases. Some of the glycosaminoglycan (GAG) preparations are sold as single products, others as various mixtures of these ingredients, and other natural products (nutraceuticals, herbal remedies).[1] The evidence for their effectiveness in the 'relief' of symptoms of pain and inflammation found in the literature and the media is often based on a selection of research and other publications that are often of dubious value or credibility.[1–3] Attempts by Professor Edzard Ernst[4,5] and others (e.g. Reichenbach *et al.*,[6] Vangsness *et al.*[7]) to apply stringent scientific criteria and evidence-based assessment of the efficacy and safety of these various GAGs and other natural products for use in arthritic diseases (principally osteoarthritis, OA) are laudable. The biological basis for the actions of many such products

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has also been questioned.[8] However, many evaluations of the CS (and indeed other GAG) products have in the past lacked evidence of: (a) pharmaceutical composition and purity, and (b) the evidential basis of clinical effectiveness linked to pharmacological activities.[9–14] The lack of clear evidence for effectiveness of mixtures of CS with other products is also noteworthy.

The requirements for comprehensive pharmaceutical analysis of any natural products sold either as non-prescription/over the counter or under some basis of prescription are mandated in many countries, yet this is rarely presented in product information or manufacturer's data. This problem of pharmaceutical composition and purity is no better highlighted than with the history concerning CS (and indeed GS or GH).[14] For example, in one study it was found that of 32 supplements available in the USA, only five contained the labelled amount of CS within an acceptable 10% limit of variation, and 17 of 32 had less than 40% of the labelled amounts of CS according to United States Pharmacopeia (USP) standards.[12] Also, a significant number of these CS products had differences in structural organisation of CS and presence of hyaluronan impurities.[12]

The review by Professor Volpi in this issue of the Journal[15] gives important insights into the chemical and pharmaceutical composition of CS products, including the following key points. (i) CS products can be derived from a variety of sources (bovine, porcine or shark) and these can have a variety of biochemical components as GAGs, each with its own physicochemical properties. (ii) Many CS products sold over the counter or used in clinical trials do not contain stated or sufficient amounts of CS. In some cases, small quantities of hyaluronic acid or other components may be present. (iii) There is a need for the CS product to be standardised. A standard is available in Europe (Bioiberica SA)[16] but few CS products that have been sold commercially in the past are properly standardised.

The use of non-standardised CS preparations in clinical trials may explain why negative assessments of their efficacy (for examples see reviews by Deal & Moskowitz,[9] Hungerford & Valaik,[10] Distler & Anguelouch[17]) and why evaluation by agencies such as the US Food and Drug Administration or in reviews has concluded that the evidence for their effectiveness is unconvincing.[18,19] The situation has now changed, however, and, as reviewed by Volpi,[15] the availability of preparations of specified quality whose pharmacokinetics and pharmacological properties have been extensively evaluated has made it possible to conduct clinical trials which have shown that CS may in fact provide benefit in OA. Until recently, however, the clinical benefits have not been clear.

Symptom-modifying changes by chondroitin sulphate

Clinical trials have not shown positive outcomes for several reasons. Among these are indications from meta-analysis by Reichenbach *et al.*[20] that trial sizes and quality may have limited the evaluation of outcome measures. Their trial selection for meta-analysis was based on data acquired from the Cochrane Central Register of Controlled trials as well as MEDLINE, EMBASE, CINAHL and other literature, some dating from 1966, or later sources up to the end of November 2006, and would not have included a considerable number of studies performed in the past 3 years. These authors did not work with raw data, the trials had mixed endpoints and timescales and, most importantly, they did not specify or evaluate trials that were performed with the Bioiberica-standardised product (e.g. Condrosulf, Institut Biochimique SA, Lugano, Switzerland). Their conclusion about trial size is, however, particularly relevant.

While some, but not all, of the earlier trials were conducted with relatively small numbers of patients, collectively they add up to a comprehensive view which shows that, overall, the standardised CS product (Condrosulf) is efficacious in the treatment of OA of the knee (e.g. see also reviews and meta-analyses by Morreale *et al.*,[21] Bourgeois *et al.*,[22] Bucsi & Poór,[23] Deal & Moskowitz,[24] and Leeb *et al.*[25]). Generally, CS was found to be about 50% more effective in relief of pain or joint symptoms than placebo.[25] In their review of the American College of Rheumatology and European League Against Rheumatism Guidelines for treatment of OA, Hochberg and Dougados[26] observed that while the effect size in OA trials of CS (like that of glucosamine and diacerhein) was smaller than that of non-steroidal anti-inflammatory drugs (NSAIDs), the onset of relief of symptomatic effects was delayed by 4–6 weeks, but, interestingly, these were maintained after stopping CS therapy. These observations are important in highlighting the slow but persistent effects of CS. Understanding of the pharmacokinetics of CS (see below) may explain why CS accumulates slowly in the synovial compartment and exhibits 'tropism' towards cartilage[27] and it may be that the pharmacodynamic effects produce some protection against joint deterioration in OA. It is also to be noted that the mechanism of action of NSAIDs, particularly on pain pathways, would be expected to be more related to the *direct* relief of painful symptoms whereas that of CS may relate more to the prevention of structural deterioration of affected joints in OA (see later section on pharmacokinetics (bioavailability) and pharmacodynamics). Thus, the symptom-relieving effects of CS may not be entirely comparable with the more rapid symptom relief provided by the NSAIDs.[28]

A considerable number of randomised, double-blind, placebo-controlled trials have been performed with Condrosulf for the treatment of OA of the knee, many meeting the requirements of Good Clinical Practice (see reviews by Hochberg & Dougados,[26] Dougados[29] and Vangsness *et al.*[30]). The consensus is that CS qualifies as a 'symptomatic slow-acting drug for OA'.[29]

The most recent consensus evaluation of drugs used for the management of OA was undertaken under the auspices of the OsteoArthritis Research Society International (OARSI).[31] The consensus recommendations were produced using the validated Appraisal of Guidelines Research and Evaluation (AGREE) instrument following a Delphi exercise, and the strength of recommendation (SOR) for propositions for each modality were obtained. Of the pharmacological modalities, CS (like that of GS) was

considered to have symptomatic benefit (e.g. Western Ontario McMaster Universities Arthritis Index (WOMAC) pain and stiffness) in knee OA, with an SOR of 63% (confidence interval (CI) 44–82%). This rating contrasts with that of NSAIDs and paracetamol (>4 g/day) which have SOR ratings of 93% and 92%, respectively. Since painful symptoms are a major basis for the assessment of these treatments, it is not surprising that CS is rated less than these analgesic agents since, as noted above, the mechanisms of action of these agents are different. It is noteworthy that other evaluations in the form of a meta-analysis of short-term (4 weeks) therapy for OA of the knee give lower rating for paracetamol which are comparable with those of CS and GS, although NSAIDs have higher ratings.[32]

Consistent findings with treatment with CS have been that (a) adverse effects are little or no different from placebo, and these are all non-serious; (b) there is reduced usage of NSAIDs and gastroprotective agents; and (c) cost–benefit assessments are in favour of treatment with CS.[25,30,33] The lower intake of NSAIDs by patients receiving prescriptions for CS400 was also shown in a cross-sectional study of pharmacies in France.[34] In a study in Russia, use of NSAIDs was also found to be reduced in patients who received CS (Struktum),[35] and in another 'office-based' study in Austria by Leeb *et al.*[36] Another recent study in Russia has shown that quality-of-life indices showed that patients who received CS (Struktum) faired better, along with joint and pain parameters.[37] One feature of the study by Lazebnik & Drozdov[35] is that CS was more effective in patients with Stages 1 + 2 Kellgren–Lawrence (K–L) scores of severity of joint destruction in OA (mild–moderate joint damage) than those with more severe damage (Stages 3 + 4). Thus, disease severity appears to affect the clinical response to CS. Furthermore, a study by Goerres *et al.*[38] showed that bone mineral density (BMD) was reduced in the affected knee of patients with OA even though general whole-body BMD was generally increased in these patients. Thus, reduced BMD may be a factor aiding or co-incident with development of knee OA and this may be another factor in determining the efficacy of CS in this condition.

The GAIT study

The much-publicised Glycosamine/chondroitin Arthritis Intervention Trial (GAIT) sponsored by the US National Institutes of Health was designed to evaluate '*rigorously*' the efficacy and safety of glucosamine, CS, and the two in combination in the treatment of pain due to osteoarthritis of the knee (trial number NCT 00032890; see Clegg *et al.*[39]). This large-scale trial in which 1583 patients were randomised to five treatment groups of 313–318 patients was, surprisingly, seriously flawed by a number of methodological and other problems. Among these was that 20–25% of the patients withdrew from the study, leaving open the question of the strength of statistical evidence from this study. This trial extended for 24 weeks and showed that neither GH, 500 mg three times daily, nor sodium CS (Bioiberica standardised), 400 mg three times daily, were significantly different from placebo in the symptomatic relief of knee pain by 20%. The rate of response assessed by WOMAC scores and pain relief was, however, significantly greater with the combined treatment with CS and GH, as was celecoxib (200 mg/day), the positive control.

Inspection of the pair-wise comparisons of the overall likelihood of a response in the pain subscales where function or pain had been predetermined as at least 50% (shown in Figure 2 in this study[39]) indicates that the 98.3% CIs overlap considerably. This suggests that there may have been little clinical difference between the treatments; this is a surprising outcome, given that celecoxib was used as the positive control.

Some authors have criticised the trial for its high rate of placebo reactors,[14,40,41] although this is a common occurrence in OA studies with slow-acting agents,[42] as well as other methodological issues.[14,41,43] The occurrence of placebo reactions (60% response) may have masked the true treatment effects.[40] This could have arisen, in part, because an exceptionally high daily dose of 4000 mg of paracetamol (acetaminophen) was allowed as rescue medication which, if taken as a full amount alone, would have provided significant relief of joint and pain symptoms. The actual average intake of this drug ranged between 1.2 and 1.7 500 mg tablets throughout all groups, which itself is likely to have some pain relief.

Lamari[14] noted that upon careful analysis the treatment effects were more substantial in the subgroup of patients with moderate-to-severe pain. This is probably due to the statistical probability of finding a greater difference (delta effect) when the pain is greater (as in this group) compared with that when there is less pain.

An intrinsic flaw in the study design may also have affected the conclusion that combined treatment with CS and GS may produce greater effect that these treatments alone – it could be argued that since CS and GH have similar effects in modifying cartilage and bone, they should have been tried at double their respective doses *as single treatments* in order to establish comparability in effect.

Subsequent analysis, re-evaluation or reviews of the results from the GAIT study have been undertaken by several authors.[14,40,43,44] Among these is a post-hoc analysis of patients with mild joint swelling and lower K–L grade at entry, in which CS showed a statistically significant improvement in joint swelling. Moreover, in patients who had moderate-to-severe pain, in 20% responders CS provided 61.4% pain relief, and those in the Outcome Measures in Rheumatology Clinical Trials (OMERACT)–OASI responder category showed 58.6% response, thus indicating that the drug gave better response in patients with more severe OA. Of course these post-hoc assessments are limited by not being predetermined outcome measures, and there may be problems relating to compromising power of the responder groups in this study.

Several authors have commented on the GAIT study but it is interesting that despite the negative outcomes of the data presented by the authors of this study (Clegg *et al.*[39]), another recent evaluation by Bruyere *et al.*,[45] using the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, has been more positive and has given evidence of symptom-modifying effects of CS. This system is based on a sequential assessment of the quality of evidence, followed by assessment of the

benefits versus risks, and then a judgement about the strength of recommendations.

Other studies

Some evidence of persistence of symptomatic improvement with CS has been provided from the results of a randomised placebo-controlled trial in which patients received two periods of 3 months' treatment over 1 year.[46] The results showed that CS 800 mg/day produced a 36% improvement in the primary outcome measure comprising the Lesquense algo-functional index after 1 year, compared with 23% in the placebo group; similar responses were observed in the Huskisson visual analogue scores for pain. The authors concluded that this study supports the prolonged effect known with symptom-modifying agents of the CS group.

Structure-modifying effects

Radiological evidence, though regarded as a best estimate of deterioration in joint structure, has to be undertaken under rigorously controlled and standardised conditions, as it is not without its problems. Given that, at best, the measures in radiological studies are of reduction in joint space width (JSW; i.e. prevention of joint deterioration) this is essentially a 'decay process', which it is envisaged is presumptively interrupted by the therapeutic agent. It is most unlikely that there will be repair processes that restore structural integrity of the joint to (near) normality. Thus, radiological observations of a preventive agent have limits in terms of what is likely to be achieved and how this will ultimately translate into improvement in joint stiffness, mobility and consequent or subsequent relief of pain. Despite the limits of assessing JSW, there have been several positive studies of the effects of CS in patients with OA of the knee or hands.

An indication of some joint protection by CS was provided by Conrozier in 1998 in a placebo-controlled investigation of 104 patients with knee OA.[47] These patients received a preparation of chondroitin sulphates-4,6. The primary outcome measure was the Lesquense score of joint function. JSW was lower in the treated group than in the placebo group.

In their 1-year interrupted-treatment study (discussed above), Uebelhart and co-workers[46] observed that the narrowing of the medial femoro-tibial joint space, involving measurements of joint space surface area, minimum JSW, and mean JSW of the pooled estimate of both knees, were all significantly different in the CS (Condrosulf)-treated than the placebo group. This provides further evidence of persistence in joint changes of structure coincident with function (as mentioned above).

Michel and co-workers[48] undertook a large-scale randomised placebo-controlled study in 300 patients who received 800 mg/day CS (Condrosulf) or placebo for 2 years. The primary endpoints in this study were the minimum and mean JSW of the more severely affected compartment of the target knee. Patients who received placebo had significant reductions in mean JSW (0.14 ± 0.61 mm (mean ± SD)) and minimum JSW (0.07 ± 0.56 mm) from baseline. In contrast, the loss of joint space was nil with both parameters in the CS group. The differences in both parameters were statistically significant: the difference between CS and placebo was 0.14 mm for mean JSW and 0.12 mm for minimum JSW. The authors claimed that the validity of the study was supported by the fact that the intent-to-treat (ITT) and per-protocol results were similar and drop-out rates were low (27%). Particular attention was paid to the positioning of joints for radiography. There was discussion of the expected joint space narrowing in patients who received placebo, based on published data; values ranged from 0.06 to 0.10 mm per annum, which appear to be approximately within the expected range. An unexpected outcome from this investigation was that although the JSW was reduced by CS, there were no significant changes in WOMAC scores. The lack of response cannot be explained.

A radiological investigation was undertaken as part of the GAIT study – a multicentre study in the USA involving 572 patents from the original study who had K–L grade 2 or 3 for OA of the knee with JSW of at least 2 mm at baseline.[49] They received the preparations as indicated above: 1200 mg/day CS alone, 1500 mg/day GH alone, or both, for 24 months. No statistically significant changes in JSW were noted in patients with K–L score of 3, but a trend towards improvement was noted in those with score of 2. The authors admitted that the power of this study was diminished by the limited sample sizes, the numbers of patients completing the study being 71, 77 and 59, respectively. The authors did suggest that patients with K–L scores of 2 might respond well to these treatments. It is clear however that more rigorous trial design could have been used in this otherwise limited study.

A recent study by Kahan *et al.*[50] examined the long-term radiographic progression and joint symptoms in a multicentre randomised trial in 622 patients with OA of the knee who received once-daily doses of CS of 800 mg, or placebo, for 2 years. This is probably the most extensive study undertaken to examine the effects of CS on joint structure. The primary outcome was change in JSW of the medial compartment of the tibio-femoral joint over 2 years. In the ITT analysis there was a significant reduction in minimal JSW in the CS group compared with the placebo group (0.07 ± 0.03 mm vs 0.31 ± 0.04 mm; mean ± SEM). This difference in JSW between the two treatments is striking and shows that joint deterioration was virtually arrested by CS. Moreover, pain reduction was faster than with placebo. The authors of this study suggested that CS could be both a disease- or structure-modifying as well as a symptom-modifying agent. Further investigation is needed to support these significant findings and should include investigations on OA biomarkers and MRI observations; nevertheless, the results are the first clear positive indications of long-term benefits of CS treatment in knee OA. With the earlier studies showing radiographic evidence of protective effects of CS in OA, these results collectively support claims for structure-modifying effects of CS in these conditions.

Hand osteoarthritis

Another interesting and significant series of observations on the effects of CS has been performed in hand OA. A study by Rovetta *et al.* reported in 2002[51] and 2004[52] evaluated the effects of CS 800 mg/day combined with naproxen 500 mg/day compared with the same dose of naproxen given alone.

Radiological examinations of the hands were performed at 1 and 2 years. These trials were in a relatively small number of patients ($n = 24$) who had erosive OA of the hand. Although the progression of erosions tended to increase with time, progression was significantly slower in the patients who received the combined treatment compared with naproxen alone. In the second report,[52] the Bouchard and Dreiser scores and the physicians' and patients' global assessment scores were higher with naproxen alone than when combined with CS.

Verbruggen and co-workers have investigated the effects of CS alone in more detail.[53–55] He developed a system for semi-quantifying radiological assessment of finger joints[53,54] which was used to determine the effects of CS.[53–55] The effects of the treatments in hand OA were graded into 'normal', 'stationary phase of OA', 'loss of joint space', 'erosive' and 'remodelling' phases. The distal interphalangeal (IP) changes were thus graded into a progression of anatomical changes. At study entry OA affected approximately 80% of distal IP and 50% of proximal IP joints of recruited patients. In approximately 40% of patients the classic picture of OA in the IP joints was complicated by massive erosive changes. A total of 165 patients were allocated to receive CS ($n = 34$), a chemically polysulphated CS ($n = 46$) or placebo ($n = 85$) over 3 years. The anatomical progression scores over 3 years were significantly lower in the CS and polysulphated CS groups than in the placebo group. Moreover, the number of patients with 'non-erosive' changes that developed 'erosive' changes was significantly lower in the CS and polysulphated CS groups than in the placebo group, and this was paralleled by assessments by both doctors and patients of global efficacy and global toxicity.

Thus, in both knee and hand OA there is, overall, clear radiographic evidence that CS has at least a delaying effect or possibly some protection against the progression of the disease in these joints. Indeed, in the evidenced-based assessment of pharmacological agents, Zang and co-workers[31] assigned a level of evidence of 1a for structure-modifying effects of CS treatment for 2 years or more, indicating the highest level of evidence. Considering the severity of the afflicted joints in the patients with OA, evidence from clinical trials for protective effects in knee and hand OA are quite striking.

Biomarkers

Mazières *et al.*[56] investigated the pain responses associated with daily activities and the Lesquense index (as primary outcomes) and biochemical markers in OMERACT-OARSI responders (secondary measures) in 307 patients who received CS or placebo for 24 weeks. Interest in this study relates to use of biomarkers of bone (CTX-I), cartilage (CTX-II) and synovial hyaluronic acid metabolism as indices of joint destruction. The investigators' assessments of efficacy and the short-form (SF-12) of physical assessment were improved in the CS groups compared with the placebo group. Although CS provided slight improvement in pain and the OMERACT-OARSI responder rate, there were improvements in bone and cartilage markers.

Pharmacokinetics (bioavailability) and pharmacdynamics

To substantiate any claims for protective or delaying effects of an anti-rheumatic/anti-inflammatory agent there must, in the classic views of Sir Austin Bradford-Hill (as recently re-evaluated), be evidence of a plausible mechanism.[57] With CS it is necessary to examine the clinical data in the context of available evidence from in-vitro and in-vivo pharmacological investigations and link this evidence to the known pharmacokinetics of the drug.

Key issues relating to the absorption of CS are *how* it gets absorbed following ingestion, and in what form does it reach or accumulate in arthritic joints where it exerts its effects? Studies with ^{3}H-radiolabelled CS given orally to rats and dogs have shown that it is rapidly absorbed, with peak levels being reached at 1–2 h, but with sustained plasma levels over 14–28 h; the radiolabel is still present in the circulation after 36 h.[58,59] Similar patterns of plasma concentrations have been obtained from studies of non-radioactive CS given to humans.[58–61] Radiolabelled CS appears in synovial fluids and cartilage[58,59] but it is not clear in what form it exists nor how much metabolism of CS occurs, although at least three fractions are present in plasma.[58] Over 70% of the dose was either excreted or localised in tissues.[58,59]

Administration of a high dose (4 g; necessary for detection of metabolites by HPLC) of bovine CS (Condrosulf) to healthy male volunteers results in peak plasma concentrations of CS averaging 12.7 μg/ml at a peak of 2.4 h and detectable levels until 8–16 h.[62] The existence of intact CS in plasma has been confirmed by agarose gel electrophoresis. There appears to be no variability in bioavailability of CS with age or sex, except with children. The absorption and bioavailability of shark cartilage is slower than that of the bovine material.[63]

In relation to molecular and cellular studies with CS, it is apparent that although the oral bioavailability of the drug is acceptable (15–24%), about 90% is depolymerised or degraded either in plasma or the joints.[60,61] Many in-vitro studies have used high and variable concentrations of CS, ranging from 12.5 to 2000 μg/ml, but generally 200 μg/ml or lower. The relationship between in-vitro pharmacological studies and what may be expected *in vivo* is therefore a matter that has still to be resolved for some target actions. This is particularly evident as, in general, only CS has been investigated for effects *in vitro* and virtually no information is available on the mixture of depolymerised or degradation products that are known to exist in inflamed joints. Nonetheless, these in-vitro investigations have provided insight into the likely actions of CS (see reviews[60,61,64–72]). Among the actions proposed from in-vitro investigations (principally using chondrocytes or cartilage explants of bovine or human origin) are: increased synthesis of proteoglycan and hyaluronic acid and aggregan, blockade of proteoglycan degradation by interleukin-1 and other pro-inflammatory cytokines and metalloproteinases, prevention of oxyradical formation, reduction in chondrocyte signalling pathways (p38, MAPK and Erk1/2, nuclear factor κB (NFκB) for example, leading to the downstream gene-regulated production of cyclo-oxygenase-2, phospholipases, cytokines, metalloproteinases),

control of apoptosis, and stress- or ageing-related changes in regeneration or repair.[73–75] Thus, it can be summarised that CS has inhibitory effects on multiple cartilage catabolic reactions whilst also enhancing anabolic processes. Several in-vivo studies in models of inflammatory joint destruction have confirmed and further established the anti-inflammatory effects of CS.[60,61,70,74]

A particularly interesting recent finding has been that CS affects the expression of the receptor activator of NFκB ligand (RANKL) in relation to the expression of osteoprotegrin (a scavenger of RANKL) in such a way as to potentially control destructive processes in subchondral bone in OA.[76]

Overall, the results of these investigations show that CS fulfils the biochemical requirements for being a biological response modifier at the level of biochemical evidence. While evidence of the effects of degradation products *in vitro* is still required, the data show that CS itself has defined effects that are unique and influence the degradative processes in OA.

Safety

One of the consistent features that have emerged from clinical trials with CS is that the incidence and severity of adverse reactions is low and in most cases little more than that observed with placebo.[30] Risk assessments for CS have highlighted that the observed safe level of intake is 1200 mg/day, which is the upper dose of this drug that is used clinically.[77] Many trials used lower daily doses of 600–1000 mg. Of the clinical trials reviewed by Hathcock & Shao,[77] the number of subjects varied, and the clinical monitoring capable of detecting adverse events ranged from self-reporting to clinical evaluation with extensive measures of haematological and clinical chemistry. There was no evidence of adverse reactions in any of the clinical trials reviewed. Patients in the GAIT study were closely monitored (see Clegg *et al.*[39]) and there were no differences in adverse reactions observed in the 635 patients who took CS compared with those in the other treatment groups (glucosamine, placebo and celecoxib).[77] There were no abnormal laboratory findings or haematological measurements in the patients who received CS. The absence of adverse reactions at any of the dose levels used in clinical trials does not enable identification of a human 'no observed effect level', however.[77]

Conclusions

It is clear that CS has considerable promise as a structurally active biological response modifier in OA. More research is needed, in particular on the relationship between pharmacokinetic and pharmacodynamic effects of CS, and detailed investigations are needed in patients with OA to establish the modes of action on joint biomarkers and MRI findings.

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