Treatment of osteoarthritis: focus on glucosamine

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Summary

Osteoarthritis (OA) is a common, degenerative disorder responsible for a high proportion of disability among the aging population. Progressing over many years, the management of OA requires multiple, successive treatment modalities. While there are many different treatments available to manage the symptoms of OA, few demonstrate reliable evidence for the long-term management of OA, and are without safety concerns. A long-term goal of OA management is to prevent or delay development of the disease with agents that have a disease-modifying effect. Symptomatic slow-acting drugs for OA (SYSADOAs) are a diverse group of medications that induce a symptomatic effect with slow onset of action, and in some cases, may induce a joint structure modifying effect in the long term. Among the SYSADOAs, the evidence is greatest for prescription-grade patented crystalline glucosamine sulfate (pCGS), which has demonstrated efficacy in control of OA pain, increase in physical function, and delay in joint structure changes in the long term.

KEY WORDS: osteoarthritis; knee; glucosamine.

Introduction

Osteoarthritis (OA) is a chronic and progressive degenerative disease, the management of which requires a long-term approach with various treatment options over the course of the disease. While many international and national evidenced-based guidelines for OA management exist, agreement is lacking on the different treatment modalities, and few prioritize the use of interventions instead providing assessment of the evidence only in absolute terms. Among the latest and more comprehensive guidelines are those from the European Society for Clinical and Economic Aspects of Osteoarthritis and Musculoskeletal Diseases (ESCEO) who provide an algorithm recommendation for knee OA, which derives from an evidence-based, expert consensus approach (1).
Systematic reviews and meta-analyses of randomized controlled trials (RCTs) provide the highest level of clinical evidence to support guideline recommendations. However, few head-to-head comparative studies are available, and most pharmacological agents are studied only for their effects on symptoms over short-term periods (≤ 12-24 weeks). We have set out to assess the available data for the relative efficacy of OA treatments, with particular focus on glucosamine for which data on long-term treatment outcomes appears most comprehensive. Reliable, comparative data on efficacy outcomes with different OA treatment modalities will help to inform future updates of treatment guidelines.

OA treatment options

In the absence of a cure for OA, there are multiple treatment modalities that can manage the symptoms of OA, however, few may be considered as disease modifying. Although widely prescribed in primary care as a first-line step for analgesia in OA, evidence does not support the use of paracetamol on a regular basis for long-term treatment. Paracetamol is demonstrated to have only a small effect on pain (effect size [ES] 0.14; 95% confidence interval [CI] 0.05, 0.22) with no effect on physical function and stiffness in knee OA patients (2). Furthermore, recent concerns regarding the safety of paracetamol raise questions over its routine, chronic use due to reports of upper gastrointestinal (GI) events, liver toxicity, renal and cardiovascular adverse events (AEs) with doses at the upper end of standard analgesic doses (>3 g/day) (3). Of particular concern is the risk of severe acute liver toxicity associated with 'staggered' overdose of paracetamol resulting from supratherapeutic doses of paracetamol (cumulative dose >4 mg/day) taken for pain relief including relief of musculoskeletal pain (4-6).
Symptomatic slow-acting drugs for OA (SYSADOAs) are a diverse group of medications that induce a symptomatic effect with slow onset of action, and in some cases, may induce a joint structure-modifying effect in the long term. SYSADOAs include mainly glucosamine, chondroitin sulfate, diacerein and avocado soybean unsaponifiables (ASU). The efficacy of SYSADOAs as a class is variable due to the diversity of agents and differing regulatory status and labelling worldwide. Thus, the ESCEO algorithm for the treatment of OA recommends SYSADOAs as Step 1 background therapy for OA, specifically with prescription-grade patented crystalline glucosamine sulfate (pCGS) and chondroitin 4&6 sulfate based upon the relative weight of evidence for efficacy and safety among SYSADOAs (1, 7). To the background SYSADOA, short-term rescue analgesia with paracetamol may be added as needed.
High quality data for prescription-grade pCGS consistently demonstrate it to be efficacious for control of OA pain (8, 9),

increase in physical function, and with evidence for disease-modifying activity in the long term (10, 11). Studies of prescription-grade chondroitin sulfate also show improvement in pain and function after 6 months with a small effect on joint structure changes (12-14). Both glucosamine and chondroitin sulfate are found to be without AEs in humans when administered in doses up to 2000 mg for glucosamine and 1200 mg for chondroitin sulfate (15). There is evidence for a small beneficial effect of diacerein on overall pain in studies of duration over 3 months, but with an increased risk of GI AEs, such as diarrhoea, mild skin reactions, and, occasionally, hepatobiliary disorders (16, 17). ASU is a complex mixture of many natural vegetable extracts, which has shown mixed results on OA symptoms and disease progression in studies of knee and hip OA, with AEs affecting the skin, liver, GI system and platelet aggregation (18-20).

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely prescribed and yet have significant GI and cardiovascular toxicity (21-23). NSAIDs should not be used for chronic treatment of OA as, beside safety issues, their efficacy is only demonstrated in the short-term (2-13 weeks) (ES 0.32; 95% CI 0.24, 0.39) (Table 1) (24). The ESCEO algorithm recommends the use of NSAIDs as Step 2 treatment, at the lowest effective dose for the shortest time necessary to control symptoms, with consideration of individual patient characteristics and medical history for the determination of which NSAID may be appropriate. Low dose celecoxib (100-200 mg/day) is associated with a lower risk of cardiovascular events compared with other cyclooxygenase-2 (COX-2) inhibitors and diclofenac (23). A recent large safety trial found celecoxib was non-inferior to naproxen and ibuprofen for cardiovascular risk, although the absence of placebo for absolute risk estimation and some methodological issues with the analysis suggest caution with consideration of the outcomes (25). In comparison, topical NSAIDs have a moderate effect on pain relief with the advantage of fewer AEs due to the lower systemic absorption, and may be used as an add-on therapy at Step 1 (26, 27).

Intra-articular (IA) corticosteroids are short-acting medications which may be of particular use if there is an effusion, although there is evidence for cartilage damage with repeated administration (28). In contrast, IA hyaluronic acid (IAHA) injection has effects on the joint lasting for up to 3-6 months, and real-life long-term data suggests that repeat cycles of IAHA injections can delay the need for total knee replacement (29). While investigation into the OA patient types most likely to benefit from IAHA is warranted, guidelines from the ESCEO and the American College of Rheumatology (ACR) recommend IAHA for knee OA in patients for whom symptoms persist despite prior treatment with analgesics (paracetamol and NSAIDs) and SYSADOAs (1, 7, 30).

Evaluation of relative efficacy of OA treatments in the long term

Recent trials and meta-analysis techniques allow assessment of single and comparative OA general treatment efficacy. Traditional pairwise meta-analyses provide information for one treatment only *versus* a single comparator; thus, interpretation of the evidence may be difficult in the perspective of appropriate disease management. Network meta-analyses integrate direct evidence from head-to-head trials (if existing) with indirect evidence comparing different treatments through their common reference. For example, a network analysis performed by Bannuru et al. of different treatment comparisons for knee OA pain after 3 months of treatment found all other OA therapies to be superior to paracetamol, a weak analgesic (32). Among NSAIDs, diclofenac had the largest effect size (ES 0.52; 95% credible interval [CrI] 0.34; 0.69), and celecoxib the smallest effect (ES 0.33; 95% CrI 0.25, 0.42).

However, the majority of analyses do not address the issue of comparative efficacy in the long term. Preliminary results of the first systematic review and (network) meta-analysis of long-term (≥12 months) RCTs of any existing medications on symptoms and joint structure changes in knee OA were presented at the ACR Congress in 2016 (33). For the primary outcome of pain change from baseline to endpoint (≥12 months), a superior treatment effect compared with placebo was only observed with prescription-grade pCGS and, to a lower extent, celecoxib among 31 different interventions analysed, including SYSADOAs, NSAIDs, corticosteroids, hyaluronic acid, bone-acting agents and paracetamol. For the secondary outcome of physical function, efficacy was found only for pCGS among the 13 interventions for which long-term data were available. Three interventions (out of 16) were found to significantly reduce radiological joint space narrowing (JSN): pCGS, chondroitin sulfate, and strontium ranelate. Thus, only pCGS was consistently shown to be effective on pain, physical function and joint structure changes (disease-modifying profile), while notably other glucosamine formulations were found to be ineffective.

Table 1 - Effect of osteoarthritis medications on pain outcomes in knee and hip osteoarthritis.

References	Treatment	Effect size*	95% Confidence Interval
Zhang et al. 2010 (2)	Paracetamol	0.14	0.05–0.23
Bjordal et al. 2004 (24)	NSAIDs†	0.32	0.24–0.39
Reginster et al. 2007 (8) and Eriksen et al. 2014 (9)	pCGS	0.27	0.12–0.43
Hochberg et al. 2010 (13)	Chondroitin sulfate	0.23	0.11–0.35
Bartels et al. 2010 (31)	Diacerein	0.24	0.08–0.39
Bannuru et al. 2015 (32)	IA corticosteroids	0.32	0.16–0.47‡
Bannuru et al. 2015 (32)	IA hyaluronic acid	0.34	0.26–0.42‡

** Effect size compared with oral placebo, with the exception of IA treatments where effect size is reported* versus *IA placebo; †Short course of treatment for 2-13 weeks; ‡95% Credible interval; IA, intra-articular; NSAID, non-steroidal anti-inflammatory drug; pCGS, patented crystalline glucosamine sulfate*

Why is glucosamine formulation important?

Glucosamine is available worldwide in multiple forms as both a prescription-grade product and over-the-counter medicines and dietary supplements which contain various quantities of glucosamine. However, although all these preparations claim to deliver a therapeutic level of glucosamine they are not all supported by clinical evidence of efficacy (34). Most non-prescription grade products contain glucosamine hydrochloride (GHCl) or GHCl plus sodium sulfate, as glucosamine sulfate itself is highly unstable under normal conditions (35).

Prescription-grade pCGS is a uniquely stabilized formulation able to deliver maximised bioavailability of glucosamine in humans (at 44%) and high glucosamine concentration in plasma (36). Studies in human chondrocyte cell lines show that pCGS inhibits the effect of a potent pro-inflammatory cytokine (IL-1β) on the expression of inflammatory markers and matrix degradation markers, thus reversing joint-degenerating effects on osteoarthritic cartilage and chondrocytes (37). The maximal effect on human chondrocyte cells is achieved with a concentration in the range of 10 uM, which corresponds to the magnitude of glucosamine concentration achieved in human plasma following pCGS administration (1500 mg) (37, 38). In contrast, the peak plasma concentration of glucosamine achieved after a single dose of GHCl (1500 mg) is considerably lower at around 2.7 uM (39).

Glucosamine efficacy

That different formulations of glucosamine should result in different efficacy outcomes has led to some discussion in the scientific community and further analysis of the available data. A Cochrane review of all glucosamine formulations studied in 4,963 OA patients, failed to show any benefit of products containing GHCl or GS (GHCl plus sodium sulfate) on WOMAC pain (Western Ontario and McMaster Universities Osteoarthritis Index), when limited to 7 high quality trials (i.e. with adequate allocation concealment) (40). Conversely, when 3 high quality trials using the pCGS formulation were analyzed in isolation, pCGS was found to be superior to placebo for WOMAC pain and function (40).

These findings were confirmed by a stratified meta-analysis of 25 RCTs in 3,458 OA patients, which was performed to address the potential risk of bias due to unsatisfactory handling of the data (i.e. during randomization and concealment and statistical analyses) (9). Among the 5 studies with 'low risk of bias' performed with glucosamine formulations excluding pCGS, a non-significant effect on pain reduction was found (SMD 0.02; 95% CI -0.08, 0.12) (9). In contrast, analysis of the 3 'low risk of bias' studies with pCGS confirmed a reduction in pain (SMD 0.27; 95% CI -0.43, -0.12) (10, 11, 41), which was in agreement with an earlier analysis of the same 3 trials of pCGS for WOMAC pain (ES 0.27) (8). The effect size on pain for pCGS, while considered moderate at 0.27, is superior to that measured for paracetamol (ES 0.14; 95% CI 0.05, 0.22) and in the same range as that achieved with a short course of treatment with oral NSAIDs (ES 0.32; 95% CI 0.24, 0.39) (2, 24).

Glucosamine: long-term effects

Ultimately, a long-term goal of OA management is to prevent or delay development of the disease. Evidence that pCGS affords a disease-modifying effect beyond symptom control in the long term is provided by 2 trials that measured a delay in joint structure changes. Analysis of joint space width (JSW) at trial enrolment and after 3 years of treatment found a reduction in JSN with pCGS. In one study, a significant difference in JSN of 0.33 mm (95% CI 0.12 to 0.54) was observed with pCGS *versus* placebo (p = 0.003) (10). In the second study, pCGS treatment was shown to completely prevent narrowing of the joint (JSN +0.04 mm; 95% CI -0.06 to 0.14: p = 0.001) (11). A lack of progression of JSN (determined at a threshold of 0.5 mm [>0.3–0.7 mm]) has demonstrated predictive value of >90% for not having joint replacement surgery (42). In both studies, fewer patients treated with pCGS experienced predefined severe JSN (>0.5 mm) compared with patients treated with placebo: 15% *vs* 30% (p = 0.013) and 5% *vs* 14% (p = 0.05).

Long-term follow-up of knee OA patients who had participated in the two 3-year trials of pCGS and received treatment for at least 12 months revealed in a post-hoc analysis that total joint replacement (TJR) had occurred in over twice as many patients from the placebo group (14.5%) in the 5 years of follow up compared with those patients formerly receiving pCGS (6.3%; p = 0.024), demonstrating a 57% reduction in risk of TJR with pCGS (relative risk 0.43; 95% CI 0.20 to 0.92). Treatment with pCGS significantly delayed the need for TJR surgery (p = 0.026) (43).

The question of whether a long-term disease modifying agent can be effective in an OA preventive setting was investigated by the Prevention of knee Osteoarthritis in Overweight Females (PROOF) study (44). The incidence of newly diagnosed OA (measured as ≥1 mm minimum JSN) among the cohort of 204 women aged 50-60 years (with BMI ≥27 kg/m^2) was reduced by 59% over 2.5 years of follow-up (odds ratio [OR] 0.41; 95% CI -0.20, 0.85; p = 0.02) by daily administration of pCGS (1500 mg). Notably the addition of a 6-month diet and exercise program gave no significant benefit for OA prevention above that obtained with pCGS prophylaxis.

Long-term SYSADOAs and disease-modifying agents should be able to decrease the use of rescue symptomatic medications, such as NSAIDs. This is evidenced by The Pharmaco-Epidemiology of GonArthroSis (PEGASus) study (45). Adults with knee and/or hip OA consulting a rheumatologist or GP for symptom flare were assigned to a SYSADOA treatment according to the physician's or patient's choice. During up to 24 months' follow-up, SYSADOA switching, continuation or discontinuation was permitted. Among all SYSADOA treatments, including GHCl, chondroitin sulfate, avocado soybean unsaponifiables, and diacerein, only pCGS achieved a significant reduction in NSAID use of 36% (OR 0.64; 95% CI 0.45 to 0.92). The reduction in NSAID use was even greater, approaching a 50% reduction, when patients who received >4 months of treatment with pCGS were considered alone (OR 0.52; 95% CI 0.28 to 0.95).

Conclusions

Practice guidelines are informed by systematic reviews and meta-analyses of RCTs, despite their inherent limitations in the case of OA. A new systematic review and network meta-analysis of long-term RCTs in knee OA showed no evidence of efficacy for most available interventions in such a setting. The only exceptions, and with good trial quality, were found for cele-

coxib among the NSAIDs for the long-term control of symptoms, albeit with a small effect size. Prescription-grade pCGS among SYSADOAs, was shown to be consistently effective on pain, physical function and joint structure changes (disease-modifying profile) in contrast to other glucosamine formulations that were ineffective. Chondroitin sulfate and strontium ranelate showed limited effects on joint structure changes and to a lesser extent on efficacy. Overall, these results support the application of the ESCEO algorithm recommendations and may inform the future revision of other guidelines.

Prescription-grade pCGS exhibits the features of a disease-modifying agent, and current practice guidelines, such as the ESCEO algorithm, are acknowledging its role among SYSADOAs and the difference with other glucosamine formulations, based on the results of previous conventional meta-analyses. Long-term prescription of pCGS decreases the use of rescue symptomatic medications such as NSAIDs, as shown in the recent pharmacoepidemiologic PEGASus study. There are also preliminary hints that pCGS might prevent incident knee OA in an at-risk population, from the PROOF study. Given the evidence base, it appears that judicious choice of treatment, and indeed formulation e.g. with prescription-grade pCGS, is essential to maximise the impact of OA guidelines and optimize the long-term treatment of OA.

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