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Efficacy and safety of glucosamine sulfate in the management of osteoarthritis: Evidence from real-life setting trials and surveys

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ABSTRACT

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) treatment algorithm recommends chronic symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) including glucosamine sulfate (GS) and chondroitin sulfate (CS) as first-line therapy for knee osteoarthritis (OA). Numerous studies are published on the use of SYSADOAs in OA; however, the efficacy of this class is still called into question largely due to the regulatory status, labeling and availability of these medications which differ substantially across the world. Examination of the evidence for the prescription patented crystalline GS (pCGS) formulation at a dose of 1500 mg once-daily demonstrates superiority over other GS and glucosamine hydrochloride (GH) formulations and dosage regimens. Thus, the ESCEO task force advocates differentiation of prescription pCGS over other glucosamine preparations. Long-term clinical trials and real-life studies show that pCGS may delay joint structural changes, suggesting potential benefit beyond symptom control when used early in the management of knee OA. Real-life pharmacoeconomic studies demonstrate a long-term reduction in the need for additional pain analgesia and non-steroidal anti-inflammatory drugs (NSAIDs) with pCGS, with a significant reduction of over 50% in costs associated with medications, healthcare consultations and examinations over 12 months. Furthermore, treatment with pCGS for at least 12 months leads to a reduction in the need for total joint replacement for at least 5 years following treatment cessation. Thus, pCGS (1500 mg od) is a logical choice to maximize clinical benefit in OA patients, with demonstrated medium-term control of pain and lasting impact on disease progression.

Introduction

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for management of knee osteoarthritis (OA) recommends the chronic use of symptomatic slow-acting drugs for osteoarthritis (SYSADOAs), in particular prescription glucosamine sulfate (GS) and chondroitin sulfate (CS), as a first-line pharmacological treatment for slow-onset medium to long term control of symptoms [1].

There have been many studies published on the use of SYSADOAs in OA; however, the efficacy of this class still meets with controversy due, in large part to differing regulatory status, labeling and availability of these medications in separate countries and regions of the world [2]. Glucosamine, in particular, is available as prescription patented crystalline glucosamine sulfate (pCGS) formulation (Rottapharm) [3], generic and over-the-counter (OTC) formulations of GS and food supplements mostly containing the glucosamine hydrochloride (GH) salt. Glucosamine supplements vary substantially from the prescription pCGS in their molecular formulation and dose regimens; only prescription pCGS is administered as a highly bioavailable once-daily dose (1500 mg) with a documented pharmacological effect [4]. The ESCEO task force acknowledges the variance in efficacy demonstrated with various glucosamine formulations in clinical studies, and recommends that prescription pCGS should be differentiated from other glucosamine formulations [1,5].

Other international evidence-based guidelines for OA management differ in their recommendations for the use of SYSADOAs [6–9]. Guidelines from the European League Against Rheumatism (EULAR) recommend both GS and CS for symptomatic treatment of

Abbreviations: CS, chondroitin 4&6 sulfate; GH, glucosamine hydrochloride; GS, glucosamine sulfate; pCGS, patented crystalline glucosamine sulfate; SYSADOAs, symptomatic slow-acting drugs for osteoarthritis.

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OA in the European prescription environment, based upon a high level of evidence (1A) [6]. Conversely, the 2012 American College of Rheumatology (ACR) does not recommend GS or CS for knee OA [7], and the 2014 Osteoarthritis Research Society International (OARSI) guideline update gives SYSADOAs an "uncertain" status for pain control [9]. The rationale for these unfavorable and non-committal recommendations may be based upon the lack of availability of prescription medications in the USA, an apparent lack of significant effect on pain when all formulations and trials are pooled in meta-analyses, and the negative results of the National Institutes of Health (NIH)-supported trial of U.S. nutritional supplements including GH [Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT)] [2,10]. Overall, there is consensus across the guidelines to consider that GH is deprived of any benefit for symptomatic knee OA treatment. In guidelines and meta-analyses that separately assess the various formulations of glucosamine, pooled results from studies using any non-pCGS preparation fail to show benefit on pain and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) function, while pCGS is consistently rated as providing a greater benefit than placebo or active comparators such as paracetamol in the treatment of pain and functional impairment resulting from symptomatic OA [11].

Mechanism of action of glucosamine

Glucosamine is a natural constituent of glycosaminoglycans in the cartilage matrix and synovial fluid, which when administered exogenously, exerts pharmacological effects on osteoarthritic cartilage and chondrocytes [12–14]. The symptomatic as well as disease-modifying effects attributed to GS may be based upon reports of downregulation in the expression of several inflammatory and degenerative mediators resulting in attenuation of degradation of the cartilage with reduction of disease progression [15]. GS is demonstrated *in vitro* to reduce prostaglandin E2 (PGE2) production and inhibit activation of the nuclear factor kappa B (NFκB) pathway, thus inhibiting the cytokine intracellular signaling cascade in chondrocytes and synovial cells [13,14,16]. In OA, glucosamine induces reversal of the pro-inflammatory and joint-degenerating effects of interleukin-1 (IL-1) [13]. IL-1β is a potent pro-inflammatory cytokine produced in high amounts in the tissues of the OA joint, where it triggers the expression of inflammatory factors such as cyclooxygenase-2 (COX-2), inducible form of nitric oxide (iNOS), IL-6, and tumor necrosis factor-alpha (TNFα). IL-1β also induces cells to produce more IL-1β as well as matrix degradation factors, such as metalloproteinases (MMPs) and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member TSs (ADAM-TSs). Most of these genes are under the transcriptional control of the signaling pathway nuclear factor NFκB. GS at clinically relevant concentrations reduces COX-2, iNOS, and microsomal prostaglandin E synthase-1 (mPGES-1) gene expression and PGE2 synthesis after IL-1β stimulation, suggesting that glucosamine can control the cascade triggered by inflammatory stimuli [17].

Studies in human chondrocyte cell models demonstrate that pCGS inhibits IL-1-stimulated gene expression of joint degeneration mediators at concentrations in the range of 10 μM, similar to those found in plasma or synovial fluid of knee OA patients after receiving pCGS at the prescription dose (1500 mg od) [15]. pCGS exhibited a dose-dependent effect on IL-1β-induced gene expression of matrix degradation factors MMP-3 (stromelysin-1) and ADAM-TS5 (aggrecanase 2) [15]. Long-term oral administration of GS may reduce the destruction of cartilage and upregulation of MMP-3 mRNA in *in vitro* models [18]. Further, GS is a stronger inhibitor of gene expression than GH, when both are administered at 5 mM doses in a human osteoarthritic explant model [19].

Examination of the evidence base for glucosamine efficacy

Examination of the evidence base for glucosamine identifies that numerous studies of varying quality have been conducted to determine the effect of glucosamine on OA symptoms. A Cochrane review of 25 randomized controlled trials (RCTs) of all glucosamine formulations in 4,963 OA patients, limited to studies with adequate concealment (11 RCTs), failed to show any benefit of glucosamine for pain [standardized mean difference (SMD) = −0.16; 95% confidence interval (CI): −0.36 to 0.04] [11]. However, when the RCTs using the pCGS formulation were analyzed separately, pCGS was found to be superior to placebo for pain (SMD = −1.11; 95% CI: −1.66 to −0.57) and function (Lequesne index SMD = −0.47; 95% CI: −0.82 to −0.12), albeit with high heterogeneity between trials (I^2 = 92%). Conversely, analysis of those RCTs using any non-pCGS preparation of glucosamine failed to demonstrate any benefit over placebo for pain (SMD = −0.05; 95% CI: −0.15 to 0.05) or function (SMD = −0.01; 95% CI: −0.13 to 0.10) [11]. In a meta-analysis of 25 placebo-controlled trials, studies using the pCGS product had a superior outcome on pain in OA compared to other preparations of GS and GH [20].

To address the issue of high heterogeneity that may compound the positive findings for the prescription pCGS formulation, there are three pivotal trials of pCGS that have been judged to be of highest quality using the Jadad quality score for clinical trials [21,22], and independently assessed as the studies with a "low risk of bias" [20]. All three pivotal trials were long-term studies of 6 months to 3 years treatment in patients with mild-moderate pain [20,23–25], for which the calculated global effect size of pCGS on pain was 0.27 (95% CI: 0.12–0.43) without heterogeneity [20,21]. The impact of pCGS formulation on other symptom outcomes was supported by a significant effect size on the WOMAC pain and function subscale scores, and Lequesne algofunctional index; with the absence of heterogeneity (Fig. 1) [21].

While the effect size for pCGS on pain may be considered as moderate at 0.27, it is greater than the effect size reported for paracetamol (0.14; 95% CI: 0.05–0.22) [26], which is recommended as short-term rescue analgesia for OA [1]. Few studies have directly compared pCGS with paracetamol, since paracetamol is often used for rescue analgesia in clinical trials; in one RCT of 6 months treatment, the effect size for pCGS (1500 mg od) on WOMAC pain was 0.25 (95% CI: −0.03 to 0.52) compared with 0.15 (95% CI: −0.12 to 0.42) for paracetamol (3 g/day), demonstrating a trend for superior effect with pCGS although it was not statistically significant [23]. In comparison to non-steroidal anti-inflammatory drugs (NSAIDs), the effect size of pCGS on pain over treatment periods ranging from 6 months to 3 years is equivalent to that achieved with oral NSAIDs, at 0.32 for pain (95% CI: 0.24–0.39) and 0.29 for function (95% CI: 0.18–0.40) for much shorter treatment courses (2–13 weeks) [27,28]. Oral NSAIDs are recommended as step two treatments in persistent symptomatic OA patients [1]. For all treatments, the balance of risk versus benefits must be considered prior to administration. Oral NSAIDs are recommended for short-term use at minimal doses for intermittent or cyclical periods due to concerns over gastrointestinal (GI), renal and cardiovascular adverse events. There is also some epidemiologic evidence for an increased risk of GI adverse events with paracetamol use, including elevation in liver enzymes [26]. Conversely, GS may be taken safely in the long term with an adverse event rate comparable to that of placebo [11].