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## EDITORIAL

### The Efficacy of Glucosamine Sulfate in Osteoarthritis: Financial and Nonfinancial Conflict of Interest

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Glucosamine has attracted a lot of interest as a specific drug for osteoarthritis (OA). Pharmacologic treatment of the disease is in fact dominated by the use of nonspecific analgesics or antiinflammatory agents, including nonsteroidal antiinflammatory drugs (NSAIDs) that have shown modest, although sound, symptomatic efficacy over short-term treatment courses, but no relevant effect during long-term use (1) and a poor risk/benefit ratio (2). Conversely, glucosamine appears to be safe (3). In addition, well-conducted clinical research with a particular form of glucosamine sulfate has shown clinically relevant symptom modification over medium-term treatment of knee OA (4). This symptom modification is sustained for years, and there is an intriguing suggestion of possible disease (structure) modification (5,6). These long-term effects are particularly relevant (7), given the chronic and progressive nature of this degenerative joint disease.

Several reviews and meta-analyses have scrutinized the efficacy of glucosamine. At least 3 of these

have emerged as being worthy of attention: a most important Cochrane Review first released in 2001 and updated in 2005 (8), a meta-analysis from our group that had the merit of being the first to include the long-term trials of glucosamine sulfate (9), and finally, 2 meta-analyses from a group in Boston. The Boston group's first meta-analysis was published in 2000 (10), but its usefulness is limited because it was performed before all of the most relevant trials with glucosamine. Vlad and coworkers have now updated their meta-analysis, and it is published in this issue of *Arthritis & Rheumatism* (11).

All these meta-analyses suggest the efficacy of at least 1 particular formulation of glucosamine sulfate, which is a prescription drug in Europe. Actually, the recent European League Against Rheumatism practice guidelines for knee OA assign to glucosamine sulfate the highest level of evidence, 1A, and strength of the recommendation, A, acknowledging the high quality of the studies performed (12). In contrast, Vlad and coworkers dismiss the quality of the most important glucosamine sulfate trials, as well as the major differences in glucosamine forms, products, dosages, and trial designs, and support only a view of bias due to industry involvement (11), a conclusion I find to be inaccurate and misleading.

There are therefore 2 aspects of this issue that deserve attention. The first is of course the actual role of industry bias in clinical research, and the second is an understanding of why the findings of the meta-analysis by Vlad et al are of concern.

#### Industry involvement in clinical research

Industry involvement is usually a predictor of more positive results. The research referenced by Vlad et al is comprehensive in acknowledging this fact. How-

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ever, as noted in a recent editorial on cyclooxygenase 2 inhibitor programs (13), industry control of most aspects of a study does not necessarily affect the credibility of the results. There are several other plausible and legitimate reasons why industry participation may give results that are different from, and more positive than, those of independent research. The first is the study design. Pharmaceutical companies have experienced clinical pharmacologists who can design trials that are better suited to showing the efficacy of a certain drug because they avoid the influence of confounders. This sometimes has the drawback of limiting the use of the drug to defined patient characteristics or clinical situations and should satisfy a demand from regulators or academia that drugs not be used beyond the indications for which they were studied. On the other hand, less carefully designed clinical research, not performed by the industry, is more likely to have several confounders and yield null results.

A second reason for different results in cases of industry participation is quality. Pharmaceutical companies are obliged to follow the principles of Good Clinical Practice (GCP), an international and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials that provides public assurance that the clinical trial data are credible (14). In addition, compliance with GCP avoids confounders, but this standard is seldom adhered to by investigators performing research outside the industry, due to the lack of the enormous financial and human resources required.

In their meta-analysis, Vlad et al deal with industry participation in glucosamine trials as an undue accident, since they only report that the substance is classified as a dietary supplement in the US, and the supplement industry is often blamed for poor product quality and poor, if any, research. However, the authors fail to remind the reader that glucosamine is approved as a prescription drug in all European Union countries and in more than 50 other countries worldwide, thanks to the studies performed by Rottapharm (Monza, Italy) with a particular form of glucosamine sulfate. As is the case with any prescription drug, for glucosamine sulfate, the most relevant clinical trials are those initiated by, participated in, and funded by the pharmaceutical company that has spent years and millions of dollars to study, patent, and develop that particular compound or product, with the numerous concomitant obligations required by the regulatory authorities. While independent data analysis of industry-supported studies is desirable (13), more advanced solutions are difficult to achieve. In fact,

it is not clear who should fund and supervise the organization, performance, and monitoring of studies that are of primary interest to the industry. A new constructive collaboration between academic medicine and industry should be promoted, but articles such as that by Vlad et al may serve to impede such mutually beneficial efforts.

### **Heterogeneity and quality in OA/glucosamine trials**

The argument of the Boston group is that there is much heterogeneity among glucosamine trials, especially if there is industry participation, that disappears in purported independent studies that, by the way, provide null efficacy results. I find fault with 2 aspects of this argument.

The first is that significant heterogeneity is common, if not the rule, in meta-analyses of drug trials in OA, and it is usually dealt with by subgrouping the trials for homogeneous characteristics. This happened, for example, with viscosupplementation, and it was solved by subgrouping for hyaluronic acid type (15); with rofecoxib, it was solved by subgrouping by dose (16); and, more generally, with NSAIDs, it was solved by pooling by design characteristics (1). In order to do this, one needs to perform a systematic review and appreciate the differences among trials, but this was not done by Vlad et al.

Second, it is obvious that studies with negative results will never show heterogeneity, since, by definition, they will all concentrate around a very homogeneous null effect. The real problem is that a systematic review should be able to show whether they had any chance of showing any efficacy.

In this respect, we agree with Vlad and coworkers on at least 1 conclusion, that 500 mg of glucosamine hydrochloride 3 times a day does not seem to be effective. We probably did not need a meta-analysis to achieve such a conclusion, since this was very clear from the results of the only 2 high-quality trials performed with this form of glucosamine: the study by Houpt et al (17) and the recent Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) (18). In the editorial accompanying the GAIT report, Hochberg actually expressed regret that the GAIT investigators had not used glucosamine sulfate, in light of the results of the studies by Rottapharm (19). The third trial of glucosamine hydrochloride cited by Vlad et al (i.e., the study by McAlindon et al [20]) is not valid since it was designed for a different purpose (21), and the protocol specifically prevented assessment of the effectiveness of glucosamine. This is

**Table 1.** Features and quality of Rottapharm-supported pivotal trials of 1,500 mg of glucosamine sulfate taken once a day for treatment of knee osteoarthritis\*

Author, year (ref.)	Trial duration, months	No. of subjects randomized	Jadad quality score	Allocation concealment†	Primary symptom outcome‡	Secondary symptom outcome
Herrero-Beaumont et al, 2007 (4)§	6	210	5/5	Adequate	Lequesne index	WOMAC score
Reginster et al, 2001 (5)	36	212	4/5¶	Adequate	WOMAC score	–
Pavelka et al, 2002 (6)	36	202	5/5	Adequate	Lequesne index	WOMAC score

\* WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

† According to the method of Rochon et al (39).

‡ Change from baseline.

§ The Glucosamine Unum In Die Efficacy (GUIDE) trial.

¶ As reported in the Cochrane Review, although all methods are appropriate and would yield a Jadad score (41) of 5/5.

curious; we expect industry to strictly adhere to protocols and several other quality standards, but the same expectations and obligations are apparently not applied to some independent research.

Quality and trial design issues should also be considered when claiming that purported independent trials of glucosamine sulfate also yielded null results when compared with industry-sponsored studies. These issues could be summarized for at least 3 studies.

The trial by Cibere et al (22) allocated >35% of patients to  $\leq 1,000$  mg/day glucosamine, a dosage that is one-third lower than the approved dosage of 1,500 mg/day. In addition, the randomization/withdrawal design used by those investigators is inadequate for drugs for which a carryover effect is hypothesized, such as for glucosamine (23); indeed, almost 60% of their patients did not have disease flares during the 6 months following the open-label glucosamine run-in period. In addition, the study was underpowered ( $\leq 70$  patients/group), and there were severe imbalances in patient characteristics at baseline (sex and disease severity) in favor of placebo. The trial by Rindone et al (24) was severely underpowered ( $< 50$  patients/group); it enrolled only men, who by the authors' admission, were older, heavier, had disease of longer duration, and had more severe radiographic changes than those in any other glucosamine studies. Fifty-seven percent of these patients were unresponsive to NSAIDs/analgesics, which were continued throughout the study. The trial by Hughes and Carr (25) was small (40 patients/group), and its power was severely challenged further by enrolling patients with all degrees of severity of knee OA (including >20% patients with intractable disease, with Kellgren/Lawrence grade 4 [26]), with more than half of the patients continuing their NSAID/analgesic medication, with a strong placebo response.

### Glucosamine formulations and dosages

Most importantly, all these studies with null results used unknown formulations of the dietary supplement glucosamine sulfate, and the inconsistency of active ingredients in commercially available glucosamine sulfate is well recognized (27). Moreover, there are different molecular forms of glucosamine sulfate (28), some of which cannot be used in pharmaceutical preparations unless they are stabilized (e.g., as in forms patented by Rottapharm [29]). Finally, all of them are used at a dosage of 500 mg 3 times a day. As a global result, their pharmacokinetic behavior (which has never been studied) might be different from that of the Rottapharm formulation.

Vlad et al mention the possibility that the Rottapharm formulation might indeed be more efficacious than the others. Moreover, a panel of experts recently met and commented on the data that support this hypothesis (30). These data include higher plasma concentrations of glucosamine with the Rottapharm product (31) than with the product used in the GAIT (32,33), as well as a strong correlation of these plasma concentrations with synovial fluid levels (34) in a range that is effective in vitro in inhibiting interleukin-1-induced gene expression (35). The latter mechanism (36) has replaced an older hypothesis of direct stimulation of glycosaminoglycan synthesis that may contribute only marginally, if at all, to the overall effect (37), unless through the availability of sulfate ions (38).

The apparent superior profile of the Rottapharm product might also be due to the special once-a-day formulation, as emphasized in the Glucosamine Unum In Die [once a day] Efficacy (GUIDE) trial, recently reported in *Arthritis & Rheumatism* (4), in which 1,500 mg of glucosamine sulfate once a day tended to be more

**Table 2.** Summary effect sizes (with 95% CIs) of WOMAC total scores (change from baseline) in the 3 Rottapharm-supported pivotal trials of 1,500 mg of glucosamine sulfate taken once a day for treatment of knee osteoarthritis\*

Author, year (ref.)	No. of subjects randomized	Weight, %	Change in WOMAC total score, mean $\pm$ SD		Fixed-model effect size (95% CI)†
			Glucosamine sulfate	Placebo	
Herrero-Beaumont et al, 2007 (4)‡	210	34	12.9 $\pm$ 14.1	8.2 $\pm$ 16.0	0.31 (0.04–0.58)
Reginster et al, 2001 (5)	212	34	229.6 $\pm$ 347.5	101.0 $\pm$ 458.4	0.32 (0.04–0.59)
Pavelka et al, 2002 (6)	202	32	8.0 $\pm$ 8.7	4.9 $\pm$ 8.2	0.37 (0.09–0.64)
Total	624	100	–	–	0.33 (0.17–0.49)

\* 95% CI = 95% confidence interval; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

† Effect sizes >0.00 favor glucosamine sulfate.

‡ The Glucosamine Unum In Die Efficacy (GUIDE) trial.

efficacious than acetaminophen. This possibility of a different effect for different dose regimens was mentioned, but underestimated, by Vlad et al.

### Principles for a sound systematic review and meta-analysis of glucosamine sulfate trials

In their meta-analysis, Vlad et al state that they were not able to explain or get rid of the persistent heterogeneity in industry-funded trials. In fact, they failed to apply the principles of a sound systematic review to the meta-analysis, but instead, put together different efficacy outcomes and trial designs by mixing 4-week studies with 3-year trials, intramuscular/intraarticular administrations with oral ones, and low-quality small studies reported in the early 1980s with high-quality studies reported in 2007. One of their analyses outlined a huge change in effect size with the decade of publication; they labeled this change nonsignificant, although it is clearly one of the most important determinants of heterogeneity.

Vlad et al have used allocation concealment as an indicator of trial quality. While this approach is appropriate, they selectively assigned an “intermediate” or even “inadequate” label to some of the most important Rottapharm trials by misusing, not by misinterpreting, the method of Rochon et al (39), or by using data published in an abstract for the GUIDE trial, although a high-quality full-length report was about to be published (4).

Industry-supported trials have the great advantage of also being classified according to their “pivotal” status (i.e., whether they are used as primary proof of efficacy in the drug registration dossier given their quality, or whether they should only be considered “supportive” of the evidence). I asked Rottapharm which placebo-controlled trials are now listed as pivotal

in their registration dossier. They identified the 2 long-term trials performed by our group (5) and by Pavelka’s group (6), as well as the recent GUIDE trial performed by Herrero-Beaumont et al (4). I accessed the databases of these studies and produced a meta-analysis of these pivotal trials using the same methods as used by Vlad et al. All 3 knee OA studies are recent, high-quality trials (Table 1). The change in Lequesne index from baseline was the primary symptom outcome in the Pavelka et al (6) and GUIDE (4) trials. However, this outcome was not assessed in the trial by Reginster et al (5). Table 2 shows the results for the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (40) total scores in all 3 trials. The change in WOMAC score from baseline was the primary symptom end point in the trial by Reginster et al, and it was assessed in the other 2 trials as the principal secondary outcome. The Lequesne index data are summarized in Table 3, together with all WOMAC score results.

The results were extremely homogeneous (no heterogeneity according to the  $I^2$  calculation), since

**Table 3.** Pooled effect sizes and heterogeneity of symptom outcomes in Rottapharm-supported pivotal trials of 1,500 mg of glucosamine sulfate taken once a day for treatment of knee osteoarthritis\*

Outcome	Effect size (95% CI)†	Heterogeneity, $I^2$
WOMAC scale		
Total	0.33 (0.17–0.49)	0.00
Pain	0.27 (0.12–0.43)	0.00
Function	0.33 (0.17–0.48)	0.00
Lequesne index‡	0.38 (0.19–0.57)	0.00

\* Includes studies by Herrero-Beaumont et al (4), Reginster et al (5), and Pavelka et al (6). 95% CI = 95% confidence interval; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

† Estimates and 95% CIs from fixed-model meta-analysis method, using the pooled standard deviation in each study/outcome.

‡ Not assessed by Reginster et al (5).

these studies enrolled patients with similar disease characteristics who underwent medium/long-term courses of treatment. The effect size was consistent across the parameters, and it was  $\sim 0.30$  or slightly higher. This effect is small to medium, but it is clinically valid ( $>0.20$ ), and especially, it is of the same magnitude as that commonly encountered with other OA treatments, including NSAIDs (1). The major advantage of glucosamine sulfate over NSAIDs is that the duration of the effect ranges between 6 months and 3 years (i.e., it is not limited to an average of 4–12 weeks as with common symptomatic medications [1]), and it is therefore of major clinical relevance in the OA treatment armamentarium.

Scientists should exercise caution when interpreting studies such as the one by Vlad and colleagues (11). While potential financial conflict of interest by pharmaceutical companies should be thoroughly assessed, other forms of conflict of interest by declared independent investigators, including financial (e.g., grants) and non-financial aspects, may be at least as much a cause for concern.

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