Efficacy and Safety of Intramuscular Glucosamine Sulfate in Osteoarthritis of the Knee

A randomised, placebo-controlled, double-blind study

A. Reichelt[a], K. K. Förster[c], M. Fischer[b], L. C. Rovati[c], and I. Setnikar[c]

The University Clinic of Orthopedics[a], Freiburg/Brsg. (Fed. Rep. of Germany), Institute for Numerical Statistics GmbH[b], Cologne (Fed. Rep. of Germany), and Department of Clinical Pharmacology, Rotta Research Laboratorium[c], Monza, Milan (Italy)

Summary

Glucosamine sulfate (Dona®, CAS 29031-19-4) is a drug used in the treatment of osteoarthritis. When orally given, it is more effective than placebo and at least as effective as non-steroidal anti-inflammatory drugs in relieving osteoarthritis symptoms. The aim of this multicentre, randomised, placebo-controlled, double-blind, parallel-group study was to assess the efficacy and safety of glucosamine sulfate intramuscularly given on the same parameters.

155 out-patients with knee osteoarthritis (Lequesne's criteria), radiological stage between I and III, Lequesne's severity index of at least 4 points and symptoms for at least 6 months, were treated with i.m. glucosamine sulfate (or placebo) 400 mg twice a week for 6 weeks. Clinic visits were performed at enrolment, after a 2-week baseline, at weekly intervals during treatment and 2 weeks after drug discontinuation. Responders to treatment were considered those patients with a reduction of at least 3 points in the Lequesne index, together with a positive overall judgement by the investigator. The Lequesne index was slightly over 10 points in average in both groups at the beginning of treatment. A significant decrease in the index was observed for glucosamine compared to placebo (3.3 vs. 2.0 points in average, respectively; $p < 0.05$, Student's t-test). The responder rate in the evaluable patients was 55% with glucosamine ($n = 73$) and only 33% ($n = 69$) with placebo ($p = 0.012$, Fisher's Exact Test). According to the intention-to-treat approach, considering also drop-outs, these proportions were 51% vs. 30% ($p = 0.015$). Both local and systemic tolerability of i.m. glucosamine sulfate were good and without difference in comparison with placebo.

Zusammenfassung

Wirksamkeit und Sicherheit von intramuskulär verabreichtem Glucosaminsulfat bei Gonarthrose / Eine randomisierte, Plazebo-kontrollierte Doppelblindstudie

Glucosaminsulfat (Dona®, CAS 29031-19-4) ist ein Medikament zur Behandlung der Arthrose. Oral verabreicht ist Glucosaminsulfat wirksamer als Plazebo und vergleichbar mit nicht-steroidalen Antirheumatika hinsichtlich seiner symptomatischen Wirksamkeit. Das Ziel dieser Multizenter-Studie (randomisiert, Plazebo-kontrolliert, doppel-blind, parallele Gruppen) war, die Wirksamkeit und das Risiko von Glucosaminsulfat nach intramuskulärer Gabe zu prüfen.

Bei 155 ambulanten Patienten wurde Gonarthrose nach den Kriterien von Lequesne diagnostiziert. Als Einschlußkriterien galten: Röntgenstadium zwischen I und III, Schweregrad-Index nach Lequesne mindestens 4 Punkte, symptomatische Beschwerden mehr als 6 Monate. Den Patienten wurde zweimal wöchtenlich 400 mg Glucosaminsulfat oder Plazebo über 6 Wochen injiziert. Die Blutkontrollen erfolgten 2 Wochen nach der Eingangsuntersuchung, danach in wöchentlichen Abständen während der Therapiedauer und 2 Wochen nach Abschluß der Therapie. Die Therapie mit Glucosaminsulfat wurde als wirksam beurteilt nach einer Abnahme von mindestens 3 Punkten im Lequesne-Index und einer positiven Globalbeurteilung des Untersuchers. Zu Behandlungsbeginn lag der Lequesne-Index im Mittel etwas über 10 Punkten in beiden Gruppen. In der Glucosaminsulfat-Gruppe wurde eine signifikante Abnahme des Indexes im Vergleich zu Plazebo beobachtet (3,3 versus 2,0 Punkte durchschnittlich; $p < 0,05$ im Student's t-Test). Die Responder-Rate betrug 55% bei Glucosaminsulfat-($n = 73$) und nur 33% ($n = 65$) bei Plazebo-behandelten Patienten ($p = 0,012$ Fisher's Exact Test). Dem „intention-to-treat approach" entsprechend und drop-outs berücksichtigend war das Verhältnis 51% zu 30% ($p = 0,015$). Sowohl die lokale als auch die systemische Verträglichkeit des intramuskulär verabreichten Glucosaminsulfat waren gut ohne Unterschied zu Plazebo.

Key words: *CAS 29031-19-4 · Dona® · Glucosamine sulfate, clinical studies · Gonarthrosis · Osteoarthritis*

1. Introduction

Glucosamine is an amino-monosaccharide and one of the basic constituents of the disaccharidic units of articular cartilage glycosaminoglycans. Glucosamine exogenously given is a preferred substrate for the biosynthesis of these glycosaminoglycans, since in vitro it stimulates the uptake of $^{35}SO_4^{--}$, a marker of this synthesis by articular chondrocytes [1]. Consequently, it inhibits the uptake of labelled glucose, which is usually used for these synthesis but with a higher energy expenditure [1]. Glucosamine is a chemically defined, small molecule (molecular weight 179.17) with a pK_a of 6.91. These favourable chemico-physical properties allow a rapid distribution of the compound throughout the body and its selective incorporation in the articular cartilage after systemic (parenteral or oral) administration, as shown using ^{14}[C]-glucosamine in animal pharmacokinetic studies [2, 3].

In view of the above observations, glucosamine sulfate (CAS 29031-19-4) has been tested for further possible pharmacological activities at the level of the cartilage and other articular tissues. Indeed, preliminary reports indicated that glucosamine sulfate is not only a substrate, but can stimulate the synthesis of glycosaminoglycans [4] and even proteoglycans (including therefore the proteic moiety) [5, 6]. The latter results were recently confirmed in human chondrocytes cultures [7]. Furthermore, glucosamine protects the cartilage from the metabolic impairment provoked by some non-steroidal antiinflammatory drugs (NSAIDs) [5], as well as the chondrocytes from the lesive action of high-dose corticosteroids [8]. Finally, glucosamine sulfate showed mild antiinflammatory activities by a mechanism of action other than the inhibition of the biosynthesis of prostaglandins [9, 10].

The above pharmacological actions prompted the clinical use of glucosamine sulfate in the treatment of osteoarthritis. Indeed, different small but controlled clinical trials indicated that the drug improved the symptoms of osteoarthritis [11–16]. In most of these previous studies, glucosamine sulfate was orally given [11–13]. The activity of the drug by the oral route has been recently confirmed by two large, randomised, controlled (with placebo and with a standard NSAID such as ibuprofen), double-blind clinical trials in osteoarthritis of the knee [17, 18]. In other studies glucosamine was given by the intramuscular route [14–16], frequently in therapeutic cycles foreseeing the concomitant or subsequent oral administration of the drug. The aim of the present investigation was therefore to confirm the activity and safety of glucosamine sulfate inrtramuscularly given, on the symptoms of osteoarthritis (pain and movement limitation) in a large patient population.

2. *Material and methods*

2.1. *Patients*

155 out-patients of both sexes and aged over 18 years were enrolled in the study. They were diagnosed to have mono- or bilateral osteoarthritis of the knee (gonarthrosis) according to the clinical and radiological criteria of Lequesne [19]. Radiographs were taken at enrolment in the weight-bearing antero-posterior view, lateral and axial views. The radiological staging, from stage I to stage IV, was performed according to the classification proposed by Jäger and Wirth [20], which is a slight modification of the grading introduced by Kellgren and Lawrence [21] and that mainly considers the progressive narrowing of the joint space, the increase in subchondral sclerosis, the appearance of osteophytes and subchondral cysts. All patients were symptomatic at enrolment, i.e. with pain at rest and/or on movement and functional limitation, but without evident clinical or biochemical (ESR < 30 mm/h) signs of inflammation. Patiens had to be able to walk without aids. The clinical stage was classified according to Weseloh and Liebig [22], ranging between I (transient symptoms) and III (continuous symptoms). These symptoms had to be present at least 6 months before enrolment. The Lequesne severity index [23] had to be at least 4 points.

All exclusions indicated in the Lequesne's criteria [19] were systematically considered, with particular regard to inflammatory rheumatic diseases, metabolic arthropaties and, in any case, rheumatic diseases other than osteoarthritis. Furthermore, patients were excluded if they had a radiological stage of O or IV; recent traumas or lesions at the involved knee(s); clinically significant haematological, hepatic or renal abnormalities at laboratory screening; extreme under- or overweight (Broca index < 75 or > 150); intraarticular corticosteroids within the 2 months prior to enrolment.

The above inclusion/exclusion criteria were checked in an enrolment visit that took place 2 weeks before the start of treatment (week –2) and that included medical history and full medical examination, with particular regard to the involved knee joint(s).

2.2. *Study design and evaluations*

The study was conducted according to a multicentre, randomised, placebo-controlled, double-blind design on two parallel groups of patients.

Two weeks after the enrolment visit, the patients were randomly assigned to twice weekly intramuscular (i. m.) glucosamine sulfate or placebo treatment for 6 weeks. Clinic visits were performed at the start of treatment and at every i.m. injection thereafter (day 3 and 7 of each treatment week). A follow-up visit was performed two weeks after the end of treatment (week 8).

Efficacy was assessed at weekly intervals throughout treatment and at the follow-up visit using the algo-functional index of Lequesne [23], which is a combined score taking into account pain, maximum walking distance and movement limitation in common activities of daily living. A final overall judgement of efficacy was expressed by the investigator as "good", "moderate", "unchanged", or "worse".

Safety was assessed by routine laboratory tests (including haematology, clinical chemistry and urinalysis) performed at enrolment and at the end of the 6-week treatment period in a central laboratory (with the exclusion of ESR); heart rate, blood pressure in the sitting position and body weight were monitored at weekly intervals. Systemic adverse events spontaneously reported by the patients following a general question, were recorded throughout the study period. Local adverse events, both objective and subjective at the injection site, were closely monitored at the moment of each administration.

Ten orthopedic or rheumatologic outpatient clinics in Germany participated in the study. The ethical principles of the Helsinki Declaration (Hong Kong revision, 1989) were implemented; ethical approval was given by the Ethical Board of the Albert-Ludwigs University in Freiburg/Brsg. (FRG) and all patients gave their written informed consent to participate in the study. The trial was conducted according to the Good Clinical Practice guidelines in force in Germany when the study was started [24].

2.3. *Treatments*

The study medications consisted of sterile and pyrogen-free ampoule pairs whose contents had to be mixed before use. For verum, ampoule A contained 400 mg of glucosamine sulfate in 2 ml aqueous solution[1], while ampoule B contained 1 ml buffer solution. Placebo consisted of ampoule pairs containing 0.9 % saline solution, that were indistinguishable from verum for colour and viscosity. The final injectable solutions had also the same physiological pH.

The study medications were administered intramuscularly twice a week, for 6 weeks.

NSAIDs, corticosteroids, or other treatments for osteoarthritis were not allowed during the study, including any physical therapy. Analgesics were also prohibited, but paracetamol could be used as rescue medication in case of unbearable pain: any paracetamol intake during the study would anyway classify the patient as a "non responder" in the principal analysis for efficacy described below. Other treatments for concomitant diseases were allowed, but had to be recorded, with the exclusion of drugs to be used intramuscularly that were prohibited in order not to confuse the assessment of safety of the study medication at the injection site.

[1] Dona® injections; Rotta Research Laboratorium, Monza (Italy).

2.4. Statistics

The principal analysis for efficacy was based on the comparison of the responder rates between treatments. "Responders" to treatment were considered those patients with a decrease in the Lequesne index of at least 3 points from basal value, together with an investigator overall judgement of efficacy rated "good" or "moderate". This analysis was performed by the Fisher's two-tailed Exact Probability test, both on the patients who completed the study according to the protocol and by the "intention-to-treat" approach, that is including all enrolled patients, regardless of compliance with the protocol, or drop-out for any reason, in order to avoid a possible bias [25].

For descriptive statistics purpose, the Lequesne index data were computed as arithmetic mean and standard error: a statistical analysis for the difference between the two groups at the end of treatment was performed by the Student's t-test. Comparison between the two patient populations with regard to demographic variables was performed by the Student's t-test or the Chi-Square test, as appropriate. The rates of adverse events and of drop-outs because of adverse events were compared by the Fisher's test. The results of laboratory tests performed at enrolment and at the end of treatment were compared by the McNemar Shift analysis. All tests were performed at the 95 % significance level.

3. Results

Out of 155 patients enrolled, 79 were randomised to the glucosamine sulfate group and 76 to the placebo group. The characteristics of the patient population are reported in Table 1. It appears that the two groups were comparable with regard to sex (over 60 % females), age (the 50–65 years range being the most represented), height, body weight, knee osteoarthritis localisation (over 50 % of patients had bilateral knee involvement), radiological stage (all mild to moderate-severe stages being represented), clinical stage and duration of symptoms (the great majority of patients presenting with chronic complaints).

Table 1: Characteristics of the patient population.

	Glucosamine sulfate	Placebo
No. of patients	79 M = 27 (34 %) F = 52 (66 %)	76 M = 27 (36 %) F = 49 (64 %)
Age (yrs)	56 ± 10 (19–70)	57 ± 10 (22–75)
Age classes		
< 50 yrs	17 M = 7 F = 19	13 M = 5 F = 8
50–65 yrs	49 M = 19 F = 30	45 M = 17 F = 28
> 65 yrs	13 M = 1 F = 12	18 M = 5 F = 13
Height (cm)	167 ± 8 (152–191)	169 ± 7 (153–192)
Weight (kg)	71 ± 10 (49– 97)	74 ± 10 (53–100)
Localization		
Left	18 (23 %)	19 (25 %)
Right	15 (19 %)	17 (22 %)
Bilateral	46 (58 %)	40 (53 %)
Radiological stages		
1	22 (28 %)	16 (21 %)
2	26 (33 %)	38 (50 %)
3	23 (29 %)	15 (20 %)
Not given	8 (10 %)	7 (9 %)
Clinical stages		
1	33 (42 %)	24 (32 %)
2	39 (49 %)	46 (60 %)
3	7 (9 %)	6 (8 %)
Durations of symptoms:		
6–12 months	7 (9 %)	6 (8 %)
1–2 year	11 (14 %)	15 (20 %)
2–10 years	54 (68 %)	47 (62 %)
> 10 years	7 (9 %)	8 (10 %)

Data are reported as absolute values (with percentages in brackets), or mean ± standard deviation (with ranges in brackets). M = males, F = females.

3.1. Efficacy

73 patients in the glucosamine group and 69 in the placebo group completed the study according to the protocol and could be evaluated for efficacy. The remaining 13 patients could be included only in the intention-to-treat analysis, since they were not fully evaluable for the following reasons. Two patients receiving glucosamine and six receiving placebo dropped out early during treatment for different reasons, apparently not related to the study (e.g. change of address, change of attitude with regard to participation in a study, etc.). Three patients in the glucosamine group discontinued the study for adverse events (that are presented below). One patient in the placebo group was excluded for protocol violation, since symptoms were too mild at enrolment (Lequesne index below 4 points). A further patient in the glucosamine group was lost to follow-up after the first injection, thus neither efficacy nor safety could be evaluated.

A total of 8 patients (2 in the verum group and 6 under placebo) made use of paracetamol during treatment: they were all given a "non responder" status in the principal analysis for efficacy. As a matter of fact, only three of these patients (1 under glucosamine and 2 under placebo) experienced some actual pain relief, in any case.

According to the definitions given above and as shown in Table 2, there were 40 "responders" out of the 73 evaluable patients treated with glucosamine sulfate (55 %), while they were 23 out of 69 (33 %) in the placebo group ($p = 0.012$). Even when considering the "intended-to-treat" population there was still a significant difference between the two groups with regard to the proportion of responders: 51 % under glucosamine vs. 30 % with placebo ($p = 0.015$) (Table 2).

The trend of the Lequesne index in the evaluable patients is described in Fig. 1. The average enrolment values in the glucosamine and placebo groups were 10.1 and 10.2, respectively and they remained stable during the 2-week baseline period before the start of treatment. Glucosamine administration induced a decrease up to an average of 6.8 points at the end of the 6-week treatment course, that was statistically significant in comparison with placebo (that reached 8.3 points). The significant improvement achieved with glucosamine was maintained for the 2-week follow-up period.

3.2. Safety

Table 3 summarises the number of patients who reported adverse events and those who discontinued the study because of these adverse events. Local pain (at the injection site) was transiently reported by one patient in the glucosamine group (who was withdrawn from the study for this reason) and by two patients receiving placebo. A further patient in the placebo group complained of an haematoma after an injection, that spontaneously regressed.

A total of 5 patients in the glucosamine group and 4 in the placebo group reported systemic adverse events throughout the study. Transient nausea/vomiting was reported by 1 patient with glucosamine and 2 patients with placebo. One patient receiving glucosamine complained of painful, heavy legs, while another one (with a history of varicose veins) had also edema and withdrew from the study. Another patient in the glucosamine group suffered of a moderate skin reaction manifested by transient erythema and itching. Finally, two patients receiving placebo complained of headache episodes throughout treatment.

The difference between the two treatment groups with regard to adverse events and related drop-out rate was not statistically significant.

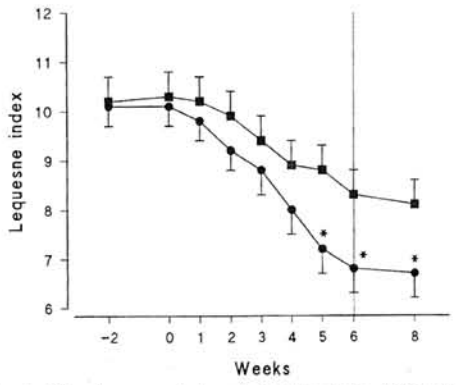

Fig. 1: Trend of the Lequesne index during the study. Values are mean ± standard error. The vertical line at week 6 represents the end of treatment. ● Glucosamine sulfate, ■ placebo; * $p < 0.05$ vs. placebo, Student's t-test.

Table 2: Number and percentage of patients who were "responders" to the treatment in the glucosamine sulfate and placebo groups.

	Glucosamine sulfate Responders		Placebo Responders		p Values
	No.	%	No.	%	
Evaluable population	40/73	55	23/69	33	0.012
"Intended-to-treat" population	40/79	51	23/76	30	0.015

The p values were calculated by the Fisher's two-tailed Exact Probability test.

Table 3: Adverse events reported during the study.

Adverse event	Glucosamine sulfate	Placebo
Local reactions	1 (1)	3 (0)
Pain/edema of legs	2 (1)	0 (0)
Pruritus or skin reactions	1 (1)	0 (0)
Nausea/vomiting	1 (0)	2 (0)
Headache	0 (0)	2 (0)
Total	5 (3)	7 (0)

The number of patients with adverse events is reported. In brackets is the number of drop-outs related to adverse events.

No statistically nor clinically significant changes were observed either in the mean values or in the individual data for laboratory tests and vital signs (data not shown).

4. Discussion

The results of this randomised, placebo-controlled, double-blind study showed that intramuscular glucosamine sulfate (400 mg twice weekly) induced a significant improvement on the symptoms of knee osteoarthritis (pain and movement limitation), over a 6-week therapeutic course. The improvement steadily developed throughout treatment and reached a statistically significant difference in comparison with placebo. The most impressive decrease in pain and functional limitation severity score started to be evident after the 3rd and was achieved between the 4th and 5th week of treatment, which is remarkable taking into consideration that the drug was given only with a twice a week frequency. This beneficial effect was maintained in the follow-up observation period.

According to the strict definition given in the present study, there were 55 % responders to glucosamine sulfate treatment compared to the around 30 % rate with placebo. This significant difference was almost identical to the one achieved in another recent trial in knee osteoarthritis, performed with a very similar study design, but in which both glucosamine sulfate (1500 mg/d) and placebo were given by the oral route for 4 weeks [17, 26]. Moreover, this 50–55 % success rate is in agreement with that of a further trial, in which a similar 4-week course with oral glucosamine sulfate yielded the same efficacy result compared to NSAIDs in patients with active knee osteoarthritis, but had a significantly better tolerability [18, 27]. Indeed, experimental studies in rats and dogs using glucosamine uniformly labelled with ^{14}C have deeply investigated the pharmacokinetics of the compound and showed its good absolute bioavailability when administered by the oral route and the special tropism for the articular cartilage [2, 3]. The latter was confirmed in similar studies performed with ^{14}[C]-glucosamine intramuscularly given to New Zealand rabbits (I. Setnikar, unpublished observation). As a matter of fact, a recent pharmacokinetic study with therapeutic doses of the labelled compound could be performed in human volunteers and directly compared the absolute bioavailability of i.m. and oral glucosamine [28]. Although the absolute bioavailability was very good after oral administration, thus confirming the previous animal and preliminary human observations [2, 3], it was practically complete after i.m. injection: this justifies the lower dose of glucosamine sulfate when given intramuscularly, such as in the present study, compared to the oral dosing adopted in the other recent trials [17, 18, 26, 27].

Nevertheless, in these latter therapeutic experiences, oral glucosamine sulfate yielded an even faster trend for improvement in osteoarthritis symptoms (2–3 weeks in average) [17, 18, 26, 27]. This observation suggests that a promising therapeutic option may be represented by the combination of the oral and intramuscular administration routes during the initial weeks of treatment, as originally proposed by previous studies [15].

Different drugs have been proposed in the past for the specific treatment of osteoarthritis [29, 30] as an alternative to the unspecific symptomatic approach represented by NSAIDs, or analgesics, or others. They have been claimed to act by different mechanisms on cartilage degeneration, including stimulation of glycosaminoglycan synthesis or inhibition of degrading enzymes, such as proteases, etc. [31–37]. For some of these drugs, a positive effect has also been reported in experimental models of osteoarthritis [38–41]. In-vitro experiments also suggested that these compounds could mimic some of the homeostatic actions on the cartilage elicited by endogenous substances, such as selected cytokines and growth factors, and they have been therefore tentatively labelled "chondroprotectives" in the past [42, 43]. This term has been then misused. In facts, no human study ever showed an ability to interfere with the disease degenerative process and clinical studies with these compounds were always focused on their capacity of improving osteoarthritis symptoms over short- or medium-term treatment courses [44–49]. Even in these latter caces, the trials were not free from methodological pitfalls and problems [50]. In this regard, the International League Against Rheumatism (ILAR) has recently proposed a draft guideline for classifying the new drugs specifically indicated for osteoarthritis management, calling them Slow Acting Drugs for Osteoarthritis (SADOA), and for testing them in clinical trials [51]. These guidelines clearly distinguish between the symptomatic activity of

SADOA and their possible, but yet undemonstrated in humans, disease modifying activity (that should replace the old and misleading term of "chondroprotection").

Indeed, glucosamine sulfate is quite different from the drugs labelled as "chondroprotectives". First of all, most of the latter are macromolecular extracts from animal cartilage, of proteic and/or polyglucidic nature, without a precise chemico-pharmaceutical definition [29, 30]. On the contrary, glucosamine sulfate is a chemically well defined and pure substance, with a small molecular weight (456.42), that in the body dissociates into sulfate ions and D-glucosamine (m.w. 179.17) and which has, beside others, the pharmacokinetic advantages mentioned above.

Secondly, glucosamine sulfate has a broader spectrum of activities [52]. Indeed, it has two basic groups of actions. The first one is centered on the articular cartilage, since glucosamine sulfate stimulates the chondrocytes to synthesise new matrix glycosaminoglycans and proteoglycans [4–7], the latter being physiological in terms of molecular weight and formation of complexes with hyaluronic acid as demonstrated by their chromatographic profiles [53]. Probably more important for its short-term symptomatic effects, are glucosamine sulfate distinct antiinflammatory properties demonstrated in different classical in-vivo models [9]. These effects are achieved without inhibiting the synthesis of prostaglandins, but probably blocking the generation of superoxide radicals and the activity of proteolytic enzymes [9]. Thanks to these activities, glucosamine was shown to be effective in animal models of arthritis [10].

Our present clinical study with glucosamine sulfate has been conducted according to the proposed ILAR guidelines for symptomatic SADOA [51]. Indeed, this trial was performed in a randomised, placebo-controlled, double-blind fashion and on knee osteoarthritis patients: other joint localisations are in fact less consistently painful and therefore less suitable for study [54]. As in a similar study performed with oral glucosamine sulfate [17], patients were enrolled on the basis of codified diagnostic criteria [19] and over 60 % of them were in radiological stage II and III, thus allowing a reliable assessment [51]. As expected, almost 70 % of patients were females and mostly middle-aged, with a 20 % proportion of elderly patients. Our subjects were chronically affected by osteoarthritis (over 80 % for more than 2 years) and more than 60 % of them had continuous or long-lasting recurrent symptoms. This patient population appears therefore to be a good representative of the general one which is commonly found in the clinical practice.

As suggested by the ILAR guidelines [51], the primary efficacy variable was based on a validated algo-functional index, namely the Lequesne index [23], and on the overall assessment by the investigator. The magnitude of the success rate achieved by glucosamine sulfate by these evaluations in our study, is in agreement with those obtained with the drug by the oral route [17, 18, 26] and, in general, with standard symptomatic treatments for osteoarthritis [23, 55]. The concomitant use of NSAIDs/analgesics was not allowed and the few patients who sporadically used paracetamol during the study, were given a negative efficacy assessment in order not to bias the net effect of the study medication.

In our study we observed a significant remanent effect of glucosamine sulfate when the treatment was stopped. Unfortunately, the follow-up period was of two weeks only, but in another study in which the drug was orally given for 6 weeks to patients with osteoarthritis of the spine, the remanent effect on pain and function was observed for further 4 weeks [56]. Other studies are in progress in order to better define the duration of the remanent effect after glucosamine treatment discontinuation [57].

The tolerability of intramuscular glucosamine sulfate was good and not different than that of placebo, in the present study. The around 5 % incidence of minor systemic adverse events is similar to that found with oral glucosamine sulfate or placebo [17, 18] and significantly lower than the one reported for NSAIDs when oral glucosamine was compared with ibuprofen in active knee osteoarthritis patients [18]. No adverse reactions that could be specifically attributed to the compounds were identified. Local tolerability at the injection site was also very good. The safety of glucosamine sulfate is supported by its mechanism of action, which does not include unspecific pharmacological actions. Furthermore, even the distinct antiinflammatory effects of the drug [9, 10] that may contribute to its clinical activity, are achieved independently of possibly lesive mechanisms of action (e.g. the inhibition of the synthesis of prostaglandins). Finally, glucosamine sulfate is a chemically defined, small (monomeric) and pure molecule, devoid of antigenic properties: in this regard, glucosamine must be clearly differentiated from extractive macromolecular anti-osteoarthritis drugs, which have been reported to cause immunologic reactions because of possible impurities [58] and to alter coagulation parameters because of their polysaccaridic nature [59].

In conclusion, the results of this study with intramuscular glucosamine sulfate confirm the positive effects obtained with the oral preparation of the drug on pain relief and functional improvement in knee osteoarthritis patients [17, 18]. Glucosamine sulfate is therefore candidate as a symptomatic Slow Acting Drug in Osteoarthritis according to the recent definition by ILAR [51], in that it selectively relieves osteoarthritis symptoms, with a few week delay in the onset of its action which is then sustained throughout treatment and tends to last after drug discontinuation. Based on these and other results [14–18, 26], a suggestion is made that the parenteral, i.m., administration could usefully complement the oral one.

Bacause of its mechanism of action on the cartilage [4–8], glucosamine is currently tested for disease modification in osteoarthritis [57] in long-term, controlled, objectively evaluated clinical trials [51].

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Correspondence: Dr. L. Rovati, Via Valosa di Sopra 7, I-20052 Monza, Milan (Italy)