

Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials

O. Bruyere Ph.D.^{†*}, K. Pavelka M.D.[‡], L. C. Rovati M.D.[§], J. Gatterová M.D.[‡], G. Giacobelli Ph.D.[§], M. Olejarová M.D.[‡], R. Deroisy Ph.D.[†] and J. Y. Reginster M.D.[†]

[†] Department of Public Health, Epidemiology and Health Economics, University of Liege, Belgium

[‡] Institute of Rheumatology, Prague, Czech Republic

[§] Clinical Pharmacology Department, Rotta Research Laboratorium-Rottapharm, Monza (MI), Italy

Summary

Objective: To assess the incidence of Total Joint Replacement (TJR) during the long-term follow-up of patients with knee osteoarthritis (OA) formerly receiving treatment with glucosamine sulphate or placebo.

Methods: Knee OA patients participating in two previous randomised, placebo-controlled, double-blind, 3-year trials of glucosamine sulphate and receiving treatment for at least 12 months, were systematically contacted to participate in a long-term follow-up retrospective assessment of the incidence of total knee replacement.

Results: Out of 340 patients with at least 12 months of treatment, 275 (i.e., 81%) could be retrieved and interviewed for the present evaluation: 131 formerly on placebo and 144 on glucosamine sulphate. There were no differences in baseline disease characteristics between groups or with the patients lost to follow-up. The mean duration of follow-up was approximately 5 years after trial termination and treatment discontinuation, making up a total of 2178 patient-years of observation (including treatment and follow-up).

Total knee replacement had occurred in over twice as many patients from the placebo group, 19/131 (14.5%), than in those formerly receiving glucosamine sulphate, 9/144 (6.3%) ($P = 0.024$, chi-square test), with a Relative Risk that was therefore 0.43 (95% confidence interval (CI): 0.20–0.92), i.e., a 57% decrease compared with placebo. The Kaplan Meier/Log–Rank test survival analysis confirmed a significantly decreased ($P = 0.026$) cumulative incidence of total knee replacements in patients who had received glucosamine sulphate.

A pharmacoeconomic analysis in a subgroup of subjects suggested that patients formerly on glucosamine sulphate had recurred to less symptomatic medications and use of other health resources than those from the placebo group during the last year of follow-up.

Conclusions: Treatment of knee OA with glucosamine sulphate for at least 12 months and up to 3 years may prevent TJR in an average follow-up of 5 years after drug discontinuation.

© 2007 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

Key words: Total joint replacement, Glucosamine sulphate, Epidemiology.

Introduction

New strategies for the treatment of osteoarthritis (OA) are directed towards the possibility of safe long-term therapies that may control disease progression. Disease Modification in OA is indeed the possibility of a treatment to prevent the disease progression and/or to reverse established OA in humans. Currently, this is identified with Structure Modification, i.e., the ability of a drug to stop or reverse the progression of joint structural damage¹. On the other hand, both the European and the US regulatory agencies require that Structure Modification translates into a significant clinical benefit for the patient before allowing a claim of a disease-modifying agent^{2,3}. In this respect, although effective Symptom Modification, i.e., the ability of the compound to improve the symptoms of the disease over the course of

the long-term clinical trial, is regarded as an important endpoint⁴, clinically relevant outcomes such as the prevention of patient's disability or of the need for surgical joint replacement, may be more solid outcomes⁵.

We recently demonstrated in two independent trials that 3-year administration of oral glucosamine sulphate 1500 mg once-a-day in a randomised, placebo-controlled, double-blind setting, prevented joint structure changes in patients with knee OA, as assessed by radiographic joint space narrowing (JSN), with a significant improvement in pain and function limitation^{6,7}. Preliminary data from the cohort of the first of these studies⁶ indicated that, during an average follow-up of 5 years after the end of the 3-year trial, patients formerly on glucosamine sulphate tended to show a decreased risk to undergo OA-related lower limb joint surgery compared with those who received placebo⁵. In order to reach a sound sample size able to give robustness to the analysis of the results, the database was merged with that of the follow-up deriving from the twin study⁷, similarly to what has already been done for reporting other outcomes⁸. The primary aim of the present study was therefore to retrospectively assess the incidence of total

*Address correspondence and reprint requests to: Professor Olivier Bruyere, Ph.D., Department of Public Health, Epidemiology and Health Economics, University of Liege, CHU Sart Tilman Bât B23, 4000 Liege, Belgium. Tel: 32-4-366-25-81; Fax: 32-4-366-28-12; E-mail: olivier.bruyere@ulg.ac.be

Received 19 April 2007; revision accepted 13 June 2007.

knee replacement during the further long-term (5 years in average) follow-up after drug withdrawal in the combined cohort of patients participating in the two previous 3-year trials^{6,7}, i.e., for a total observation of approximately 8 years.

Methods

A total of 414 patients of both genders with knee OA diagnosed according to the ACR criteria, had participated in the previous 3-year trials: 212 patients in Study 1⁶ and 202 patients in Study 2⁷. All of them were considered for participation in a follow-up evaluation to assess various endpoints and, in particular, the incidence of clinically relevant disease outcomes represented by the occurrence of total knee replacement. For this primary endpoint, only patients who had completed at least 12 months in the previous trials were included in the present analysis, in order to assure a reasonable exposure to the study medication that could strengthen any association between the treatment itself and the events during the follow-up. In addition, 12 months is the minimum treatment duration prescribed by both the European and the US regulatory agencies for putative disease-modifying agents^{2,3}.

Telephone contact was systematically attempted with all patients. If this was unsuccessful, contact was established by mail. For all patients successfully contacted, a telephone or clinic visit interview was scheduled to administer a standardised questionnaire about OA-related lower limb surgery occurring after the trial, with particular reference to total knee replacement. Information collected in the interview was checked against information from the patient's general practitioner and/or medical file.

For the primary analysis, the proportion of patients undergoing total knee replacement in the two former treatment groups, glucosamine sulphate and placebo, was compared by the chi-square test. The Relative Risk of undergoing knee arthroplasty after glucosamine sulphate relative to placebo was also calculated, with its 95% CI; the Number Needed to Treat (NNT), i.e., the number of patients that would need to be treated to avoid one knee replacement, was also calculated according to the standard method. The results on this primary outcome were confirmed in a more sensitive time-to-event (time-to-knee replacement) Kaplan Meier/Log-Rank test survival analysis.

Different secondary analyses were also performed, including an exploratory analysis of the effect of a possible predictor of the primary outcome and a preliminary pharmacoeconomic assessment.

With respect to the former, JSN of more than 0.5 mm over a 2–3-year period has been recently suggested as the joint structure change threshold to define patients that are treatment failures in a disease modification drug study, possibly reflecting a high propensity for an individual patient to later require joint surgery¹. JSN > 0.5 mm had been indeed defined as a threshold for severe structural damage progression and a potential predictor of disability in the two long-term clinical trial reports^{6,7}. Part of our group of investigators has already shown that, in the Study 1 cohort, JSN of more than 0.5 mm at the narrowest point of the medial compartment of the tibiofemoral joint (minimum JSN) during the previous trial was a good predictor of the risk of undergoing knee surgery during the follow-up period observation⁹. In the present analysis we wanted to confirm that this occurred also in the Study 2 patient cohort selected for the primary outcome. For this purpose, the patients from this latter cohort who had reached during the previous trial the JSN cut-off of at least 0.5 mm were identified. The incidence of knee replacement in these patients

was compared by the chi-square test with that observed in those not reaching such a threshold. In addition, their Relative Risk (95% CI) of undergoing knee replacement was calculated.

After the end of the trials, patients had been followed by means of standard care, including recourse to standard medications such as analgesics or non-steroidal anti-inflammatory drugs (NSAIDs) in the majority of cases and, in a smaller proportion, to putative specific agents for OA (known as chondroprotectives or slow-acting symptomatic drugs). The prescription glucosamine sulphate 1500 mg once-a-day formulation¹⁰ previously used in the two 3-year trials (Dona[®], Xicil[®], Viartiril-S[®], or other trademarks by the Rottapharm Group, Monza, Italy) was not available in Belgium (where Study 1 was performed), while it became available in the Czech Republic (where Study 2 had been running) during the follow-up observation. On the other hand, different uncontrolled dietary supplement preparations containing glucosamine were available in both countries. In addition, as mentioned above, other agents for OA that were excluded during the trials, might have been available during the follow-up, including intra-articular compounds (e.g., hyaluronic acid) or systemic agents (such as chondroitin sulphate, avocado-soybean unsaponifiables, diacerein, etc.) as either prescription drugs or dietary supplements. Due to the length of the follow-up period, it was not possible to collect precise retrospective information on medication and other intervention history after the trials. However, information was systematically collected by a standardised questionnaire for the year prior to the follow-up visit in a subset of 101 patients from Study 1 that attended a clinic visit. These patients could be evaluated in a more comprehensive assessment that included a pharmacoeconomic investigation on the use of health resources during the last year of the follow-up period. In fact, to provide a meaningful comparison between the former two groups of patients, the use of the different medications was turned into actual costs (based on national formulary reference prices). Assessment of recourse to other health resources included the number of OA-related visits to any specialist physician or paramedical operators (e.g., physiotherapists), and the number of diagnostic procedures for disease specific purposes, or evaluation of current drug treatment safety, or other general health issues. Also in this case, the actual use of the health resource for OA-related problems was turned into its cost and the total expenditure per patient per year was calculated. The resulting cost analysis consisted therefore of the assessment of direct medical costs in the perspective of the society, i.e., based on national formulary reference prices reimbursed by the National Health System. Direct non-medical costs, which are usually born by the patient (e.g., transportation, formal care provided by paid personnel, etc.) were not assessed, similarly to indirect costs (e.g., productivity loss by the patient or the informal caregiver, etc.). The comparison of the cost of health resources utilisation in the two former treatment groups was performed by the Mann-Whitney *U* test.

All evaluations and analyses were performed in double-blind conditions. In fact, patient contact attempts, interviews and possible clinic visits were performed and analysed by investigators unaware of the individual patient treatment assignment during the original trials. In addition, patients had never been told whether they had received glucosamine sulphate or placebo during the trials and they were therefore still blinded with respect to the former treatment assignment.

The study was approved by the site Ethics Committees.

Results

The patient disposition for the joint patient cohort is reported in Fig. 1. Out of 414 knee OA patients randomised in the original trials, 340 had completed at least 12 months of treatment, 168 with placebo and 172 with glucosamine sulphate, and would have been therefore eligible for the primary outcome assessment. Sixty-five of these patients were actually lost to follow-up, without apparent differences between groups. Therefore, 275 patients, i.e., 81% of the target population with at least 12 months of treatment, could be contacted and participated in this follow-up evaluation: 131 had received placebo and 144 had received glucosamine sulphate. In average, these patients had received treatment in the former trial for 32 months i.e., over 2 years and a half, ranging between the minimum requirement of at least 12 months to participate in this follow-up primary assessment, and completion of the 3-year trial period. Notably, 113 out of the 144 (78.5%) patients who had received glucosamine sulphate, had completed the 36-month treatment.

The mean duration of follow-up, i.e., from the last clinic visit in the former trial to the present evaluation was approximately 5 years, namely 63 months in the former placebo group and 62 months in the former glucosamine sulphate group, ranging from a minimum of 3 years to a maximum of up to 8 years. Overall the complete observation period, including treatment and follow-up, was for 2178 patient-years.

Table I (left panel) reports the baseline characteristics (i.e., at randomisation in the two trials) of the 275 patients participating in this follow-up assessment. Patients from the former two groups had similar demographic characteristics and mild-to-moderate disease severity, as expressed by standardised Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores between 30 and 40 on a 0–100 scale and minimum joint space width

slightly lower than 4 mm, in average. These characteristics were similar to those of the entire patient population randomised in the two original trials^{6,7}. The 65 patients lost to follow-up (Table I, right panel) tended to be slightly older, but they were similar for baseline disease characteristics, perhaps with the exception of a trend for a slightly narrower joint space in both groups and milder enrolment symptoms in the former glucosamine sulphate group, that on the other hand had slightly more function limitation and pain at enrolment in the larger cohort of the 275 patients in which the primary outcome could be assessed (Table I, left panel).

The two original trials contributed in a similar proportion to this final cohort of 275 patients: 142 patients had participated in Study 1 (65 on placebo and 77 on glucosamine sulphate), while 133 derived from Study 2 (66 placebo and 67 glucosamine sulphate). There were no significant differences in baseline demographic and disease characteristics between patients from the two trials. However, compared to patients from the latter study, those from the former tended to be slightly older (65 vs 62 years of age), heavier (BMI 27.4 vs 25.8) and more symptomatic (WOMAC pain on the 0–100 scale 36 vs 32, and WOMAC function 41 vs 33). Conversely, patients from Study 2 had slightly narrower minimum joint space width than those from Study 1 (3.6 vs 3.9 mm, respectively). These minor and non-significant differences do not seem to be of clinical relevance.

With regard to the primary outcome, out of the 275 follow-up patients, 28 (10.2%) had undergone total knee replacement during the observation period. Table II shows that there were over twice as many patients undergoing total knee replacement in the former placebo group, 19/131 (14.5%), than in the former glucosamine sulphate group, 9/144 (6.3%): $P=0.024$. The Relative Risk of undergoing knee replacement was 0.43 (95% CI from 0.20 to 0.92) for patients who received glucosamine sulphate, i.e.,

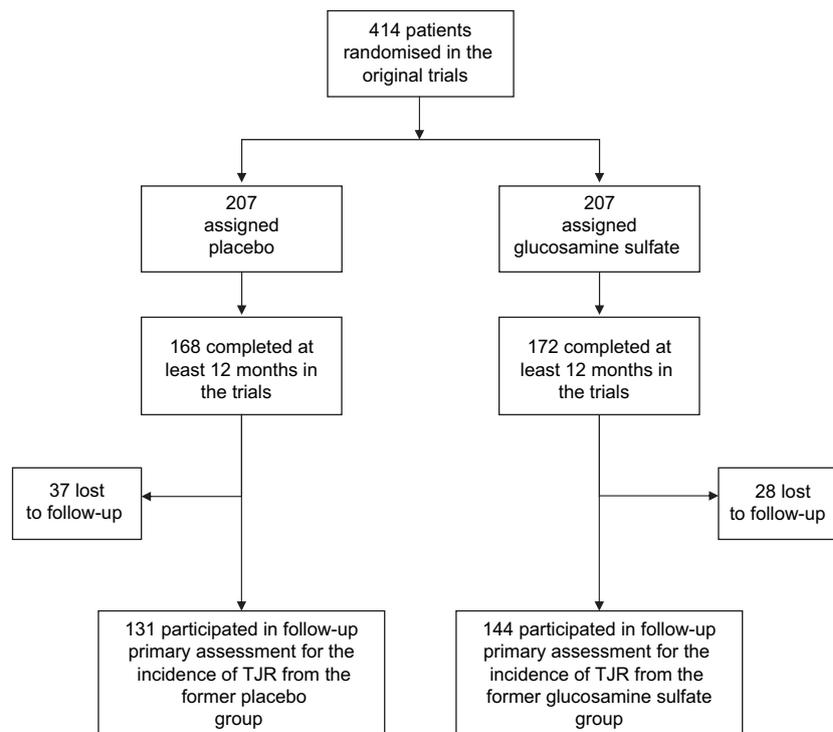


Fig. 1. Patient disposition after the end of the original trial.

Table I
Baseline (pre-trial) demographic and clinical characteristics of the patients participating in the follow-up evaluation and of those lost to follow-up

Characteristic	Patients assessed at follow-up, N = 275		Patients lost to follow-up, N = 65	
	Placebo, N = 131	Glucosamine sulphate, N = 144	Placebo, N = 37	Glucosamine sulphate, N = 28
Age – year	63.6 (6.6)*	62.9 (7.6)*	66.0 (8.9)	65.2 (10.1)
Body mass index – kg/m ²	26.6 (2.5)	26.6 (2.5)	26.7 (2.6)	25.7 (2.3)
Minimum joint space width – mm	3.83 (1.34)	3.89 (1.32)	3.71 (1.72)	3.66 (1.73)
Total WOMAC index – 0–100 scale [†]	34.8 (17.4)	38.2 (18.2)	35.3 (19.5)	30.7 (16.2)
WOMAC pain – 0–100 scale [†]	32.5 (18.0)	35.6 (18.6)	33.4 (19.2)	30.3 (15.6)
WOMAC function – 0–100 scale [†]	35.0 (18.7)	38.8 (19.6)	36.0 (20.6)	30.4 (17.0)
WOMAC stiffness – 0–100 scale [†]	38.8 (25.3)	39.8 (25.5)	33.6 (26.4)	34.1 (26.6)

Data are mean (Standard Deviation).

*Age at the moment of the follow-up observation was 70.1 (6.6) and 69.2 (7.3) years in the former placebo and glucosamine sulphate groups, respectively.

[†]Study 1 adopted the WOMAC visual analogue scale (VAS) scale version, while Study 2 had used the Likert scale version: data were normalised to the 0–100 scale before merging the databases.

a 57% decrease compared with placebo. The NNT to avoid one knee replacement was 12.

The time-to-event analysis confirmed the results of the primary outcome, indicating a significantly ($P=0.026$) decreased and delayed cumulative incidence of total knee replacements for the patients formerly on glucosamine sulphate (Fig. 2).

All patients undergoing knee replacement in the former glucosamine sulphate group but one had completed the 3-year treatment during the previous trials. Joint replacement after glucosamine sulphate was therefore apparently not associated with a shorter duration of treatment.

Similarly to what has already been described for the Study 1 patient cohort⁹, JSN of more than 0.5 mm during the 3-year trial was a good predictor of joint replacement during the follow-up in patients from Study 2. In fact, out of the 15 follow-up patients with JSN > 0.5 mm during the trial, four of them (26.7%) had undergone total knee replacement, compared with only 7.6% (9/118) of those who had not reached this cut-off of joint structure deterioration ($P=0.019$). The Relative Risk was 3.50 (95% CI 1.23–9.97), thus corresponding to an over three-fold increase in risk.

Among other secondary evaluations, an assessment of the intake of other drugs could be performed for the year prior to the follow-up clinic visit in a subset of 101 patients from Study 1. Only a minority of them had received putative specific, slow-acting drugs for OA, namely 18.6 and 17.6% in the former placebo and glucosamine groups, including only four patients reporting access to a glucosamine formulation. Conversely, analgesics (alone or in combination with the other medications) had been taken by 65.1 and 60.3%, while NSAIDs (again alone or in combination with the other agents) were accessed by 44.2 and 41.4% of patients previously on placebo or glucosamine sulphate, respectively. However, patients who had received glucosamine sulphate during the former trial had a strong trend to consume less (and thus to spend less on) drugs for OA when the information was included in the pharmacoeconomic assessment (Table III). There was no selective use of any specific

medications whose price could account for the difference observed, that was only due to a difference in consumption. When the recourse to other health resources was also assessed, it appeared that patients previously on glucosamine sulphate also recurred to less medical specialist and paramedical visits for OA and underwent fewer examinations for the assessment of drug safety (such as gastroscopies, probably because of the lower intake of NSAIDs). When all was turned into actual costs (Table III), glucosamine sulphate patients had a significant ($P=0.024$) decrease, by over 50%, in expenses compared with patients who were previously on placebo.

Discussion

In this study, patients with knee OA who had received oral glucosamine sulphate 1500 mg once-a-day for at least 12 months and up to 3 years in two previous randomised, placebo-controlled, double-blind trials^{6,7}, had a lower incidence of Total Joint Replacement (TJR) during an average follow-up of further 5 years after drug discontinuation, compared with patients who had received placebo. In particular, patients previously on glucosamine sulphate experienced a 57% decrease in the risk of undergoing total knee replacement. The time-to-event analysis showed that total knee joint replacements evenly occurred throughout the whole observation period in patients formerly in the placebo group. Conversely, they tended to occur later and at a reduced incidence in the patients who had received glucosamine sulphate.

These data refer to the systematic interview of 275 patients, corresponding to 81% of the patient population completing at least 12 months of treatment in the previous trials. Although this is a relatively large population and a high referral rate for such a long period of follow-up after trial termination, it cannot be excluded that disease outcomes from the 65 patients (19%) lost to follow-up, might alter the results reported here. On the other hand, baseline disease

Table II
Occurrence of total knee replacement during the follow-up, with Relative Risk of glucosamine sulphate vs placebo and P value

Patients/events	Placebo, N = 131	Glucosamine sulphate, N = 144	Relative Risk (95% CI)	P
Number (and %) of patients with total knee replacement	19 (14.5%)	9 (6.3%)	0.43 (0.20 to 0.92)	0.024

The NNT with glucosamine sulphate to avoid one knee replacement is 12.

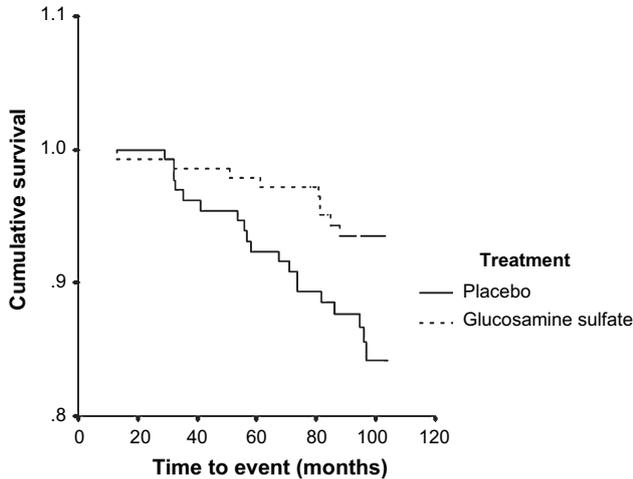


Fig. 2. Time-to-event analysis of total knee replacement in the overall follow-up population ($N=275$): $P=0.026$ (Log-Rank test).

characteristics were similar in these patients lost to follow-up and, if anything, patients in this cohort and formerly receiving glucosamine sulphate had slightly milder symptoms at trial enrolment than those participating in the follow-up evaluation, making unlikely a different pattern of worsening. Rather, patients lost to follow-up were in average older than patients participating in the primary assessment and age may have been therefore the most important determinant of the different level of referral.

Patients from the two original trials could be safely combined in the present study, since they had similar baseline demographic and disease characteristics. Merging the two cohorts gave us the opportunity to achieve a meaningful sample size to explore a possible association of the treatment with the primary outcome.

The present observation also explored whether the joint structure changes observed during the 3-year treatment

period could be used to predict the need for joint surgery. Indeed, both previous trials showed that glucosamine sulphate was able not only to decrease the rate of JSN, but also to significantly reduce the proportion of patients with severe loss, defined by a cut-off of more than 0.5 mm during the 3-year treatment period^{6,7}. A sub-analysis from the Study 1 follow-up cohort has already shown that patients with JSN of more than 0.5 mm had an increased risk of undergoing any OA-related lower limb joint surgery⁹. In the present study, these findings are confirmed on the Study 2 patient cohort, in that patients reaching such threshold during the trial, irrespectively of treatment, had an over three-fold increase in the risk of knee replacement during the observation period. While these data provide external validity to the predictive value of this cut-off for disease progression¹, they further validate the efficacy of glucosamine sulphate during the former trials^{6,7}, on a parameter that is now confirmed to be clinically relevant. As a matter of fact, the actual relevance of radiographic JSN as a measure of joint structure damage and especially of cartilage loss has been controversial. Meniscal subluxation has been indicated as the possible main determinant of JSN, but it is nevertheless associated with symptomatic knee OA¹¹. Studies with magnetic resonance imaging (MRI) suggested that position and degeneration of the meniscus may indeed account for a great part of the variability in JSN, but cartilage loss contributes at least 40%¹². In addition, these studies have shown that meniscal changes have potent effects on cartilage loss¹³ and, finally, that cartilage loss on MRI and radiographic JSN are well-correlated^{14,15}. These data seem therefore to support the clinical relevance of our previous findings on JSN, even if they had been obtained by the conventional standing antero-posterior radiographic view^{6,7}. Although this technique was state-of-the-art at the time of our trials, it was later criticised for being possibly biased by the status of knee pain or its relief¹⁶. Nevertheless, we have recently demonstrated that knee pain relief did not bias the assessment of joint space width in this population with this technique¹⁷. The present data further strengthen the validity of our previous assessment.

Conversely, while previous treatment with glucosamine sulphate was associated with a lower incidence of joint replacement, the chance of this event to occur was not apparently associated with a shorter treatment duration with the substance, since all but one of the patients who underwent surgery in the former glucosamine sulphate group, had completed the 3-year treatment in the trials. On the other hand, treatment completion occurred in the vast majority of patients and thus this study could not properly assess the effect of treatment duration.

The main limitation of the present study is that it was not possible to standardise patient's treatment after the end of the trial and to get precise information on the standard of care they received. It is not possible therefore to discriminate whether the treatment received afterwards could have influenced the primary outcome in this study. Access to the prescription glucosamine sulphate formulation used in the trials was virtually nil during the follow-up in Belgium, but might have been possible in the Czech Republic, where the two studies were performed, respectively. In addition, dietary supplement glucosamine preparations might have been available in both countries. Similarly to any other intervention for OA, use of any glucosamine preparation other than the study medication was prohibited during the 3-year trials. Moreover, use of glucosamine dietary supplements was in general discouraged in the two 3-year trial

Table III

Mean (with standard error (SE) in brackets) use of health resources per patient in the year prior to the follow-up evaluation and total cost calculated for OA-related expenses. The data refer to a subset of 101 patients from Study 1 that attended the follow-up clinic visit

Variables	Placebo, N=43	Glucosamine sulphate, N=58
Cost of analgesics – €*	59 (23)	19 (3)
Cost of NSAIDs – €	116 (31)	63 (17)
Total cost of OA† drugs – € (including analgesics, NSAIDs, etc.)†	204 (43)	108 (20)
Number of visits to specialist†	2.1 (0.5)	1.8 (0.3)
Number of visits to general practitioner	11.1 (1.5)	9.8 (1.1)
Number of paramedical visits for OA†	17.4 (6.3)	6.6 (2.0)
Number of radiographs for OA†	0.60 (0.14)	0.44 (0.09)
Number of gastroscopies†	0.30 (0.07)	0.10 (0.04)
Number of non-OA exams	5.4 (1.6)	2.8 (0.6)
Total cost calculated for OA-related resources – €	605 (21)	292 (6)§

*€ = Euro; 1 Euro = ~1.3 US\$.

†Included in total cost calculation.

§ $P=0.024$ vs. placebo.

reports^{6,7} due to the undemonstrated pharmacokinetic and treatment efficacy properties, questionable pharmaceutical characteristics and real active ingredient content of these products¹⁸.

While it was impossible to estimate how many patients had access to glucosamine or other putative OA-specific medications during the follow-up in the Study 2 cohort, and this is clearly a limitation, retrospective information could be collected for the last year of follow-up in a subset of patients from Study 1. Actually, four patients only had received any glucosamine preparation in this patient subset and they belonged to the minority of less than 20% patients receiving any so-called chondroprotectives or slow-acting symptomatic agents during the last year of follow-up, without differences between groups. Conversely, patients formerly on glucosamine sulphate had used approximately half analgesics and NSAIDs than those in the original placebo group, which would suggest an overall better control of the disease symptoms in agreement with the results of the primary outcome. This was also in agreement with a lower use of other health resources and a better global pharmacoeconomic performance for patients who had received glucosamine sulphate. Such pharmacoeconomic data are limited by being obtained only in a subset of patients and referring only to the last year of follow-up. For this latter reason they could not include the costs of TJR, whose incidence was assessed over the entire observation period. However, any cost analysis that included the costs of surgery would produce an even higher favourable effect of the previous treatment with glucosamine sulphate, given the results of the primary outcome of the present study. Such pharmacoeconomic outcome would not change even if the modest cost of this particular formulation of glucosamine sulphate (which is a patented prescription drug in Europe) is taken into account for the 3-year average treatment duration, the expense for which should be spread over the average 8 years of observation.

Another limitation is that the indication to total knee replacement might have been different in each individual patient. In addition, the actual occurrence of surgery might be driven by several confounders that are country-specific or even region-specific¹⁹, including population density, demographics and, especially, different aspects of health policy. On the other hand, this is a common limitation in studies of time to performing joint replacement. For this reason, several initiatives are exploring the feasibility of different surrogate approaches for the standardisation of the indication to surgery^{5,20}.

In conclusion, long-term (3 years) treatment of knee OA with glucosamine sulphate may prevent TJR in the longer run, according to the results of this overall 8-year observation. This outcome might be explained by the preservation of radiographic joint space during treatment and by the overall well-being that seems to result in a lower consumption in health resources. Our findings would deserve confirmation in a prospective and carefully standardised study setting.

References

1. Abadie E, Ethgen D, Avouac B, Bouvenot G, Branco J, Bruyere O, *et al.* Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. *Osteoarthritis Cartilage* 2004;12:263–8.
2. Committee for Proprietary Medicinal Products. Points to Consider on Clinical Investigation of Medicinal Products used in the Treatment of Osteoarthritis (CPMP/EWP/784/97). London: The European Agency for the Evaluation of Medicinal Products July 1998.
3. Guidance for the Industry. Clinical Development Programs for Drugs, Devices and Biological Products Intended for the Treatment of Osteoarthritis. US Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research July 1999.
4. Group for the Respect of Ethics and Excellence in Science (GREGS). Recommendations for the registration of drugs used in the treatment of osteoarthritis. *Ann Rheum Dis* 1996;55:552–7.
5. Altman MD, Abadie MD, Avouac MD, *et al.* Total joint replacement of hip or knee as an outcome measure for structure modifying trials in osteoarthritis. *Osteoarthritis Cartilage* 2005;13:13–9.
6. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, *et al.* Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomized, placebo-controlled clinical trial. *Lancet* 2001;357:251–6.
7. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacobelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med* 2002;162:2113–23.
8. Bruyere O, Pavelka K, Rovati LC, *et al.* Glucosamine sulfate reduces osteoarthritis progression in postmenopausal women with knee osteoarthritis: evidence from two 3-year studies. *Menopause* 2004;11:138–43.
9. Bruyere O, Richey F, Reginster JY. Three year joint space narrowing predicts long term incidence of surgery in patients with osteoarthritis: an eight year prospective follow up study. *Ann Rheum Dis* 2005;64:1727–30.
10. De Wan M, Volpi G, inventors. A method of preparing mixed glucosamine salts. US patent 5,847,107. 1997 Aug 13.
11. Gale DR, Chaisson CE, Totterman SM, Schwartz RK, Felson D. Meniscal subluxation: association with osteoarthritis and joint space narrowing. *Osteoarthritis Cartilage* 1999;7:526–32.
12. Hunter DJ, Tu X, LaValley M, Zhang YQ, Niu JB, Amin S, *et al.* Change in joint space width: hyaline cartilage loss or meniscal change (abstract). *Arthritis Rheum* 2004;50(Suppl 9):1717.
13. Hunter DJ, Tu X, LaValley M, Zhang YQ, Niu JB, Amin S, *et al.* The meniscus and cartilage loss (abstract). *Arthritis Rheum* 2004;50(Suppl 9):231.
14. Amin S, LaValley M, Guermazi A, Hunter DJ, Gale D, Felson D. Cartilage loss at the knee on MRI and its relation to knee radiographic progression (abstract). *Arthritis Rheum* 2004;50(Suppl 9):563.
15. Bruyere O, Genant H, Kothari M, Zaim S, White D, Peterfy C, *et al.* Longitudinal study of magnetic resonance imaging and standard X-rays to assess disease progression in osteoarthritis. *Osteoarthritis Cartilage* 2007;15:98–103.
16. Brandt KD, Mazzuca SA, Conrozier T, Dacre JE, Peterfy CG, Provvedini D, *et al.* Which is the best radiographic protocol for a clinical trial of a structure modifying drug in patients with knee osteoarthritis? *J Rheumatol* 2002;29:1308–20.

17. Pavelka K, Bruyere O, Rovati LC, Olejárova M, Giacobelli G, Reginster JY. Relief in mild-to-moderate pain is not a confounder in joint space narrowing assessment of full extension knee radiographs in recent osteoarthritis structure-modifying drug trials. *Osteoarthritis Cartilage* 2003;11:730–7.
 18. Russell AS, Aghazadeh-Habashi A, Jamali F. Active ingredient consistency of commercially available glucosamine sulfate products. *J Rheumatol* 2002;29:2407–9.
 19. Dieppe P, Basler HD, Chard J, Croft P, Dixon J, Hurley M, *et al.* Knee replacement surgery for osteoarthritis: effectiveness, practice variations, indications and possible determinants of utilization. *Rheumatology (Oxford)* 1999;38:73–83.
 20. Maillefert JF, Hawker GA, Gossec L, Mahomed NN, Lohmander S, Dieppe PA, *et al.* Concomitant therapy: an outcome variable for musculoskeletal disorders? Part 2: total joint replacement in osteoarthritis trials. *J Rheumatol* 2005;32:2449–51.
-