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Effects of glucosamine sulfate on the use of rescue non-steroidal anti-inflammatory drugs in knee osteoarthritis: Results from the Pharmaco-Epidemiology of GonArthroSis (PEGASus) study☆

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ABSTRACT

Background and objective: The use of Symptomatic Slow-Acting Drugs in Osteoarthritis (SYSADOAs) may be expected to decrease the use of concomitant medications for rescue analgesia, including non-steroidal anti-inflammatory drugs (NSAIDs). The Pharmaco-Epidemiology of GonArthroSis (PEGASus) study was designed to assess this possibility.

Methods: PEGASus was a cohort study of continuous recruitment of patients with "dynamic" exposure to the investigated SYSADOA (crystalline glucosamine sulfate, glucosamine hydrochloride, chondroitin sulfate, diacerein, and avocado–soybean unsaponifiables, all at approved dosages). Investigators were rheumatologists or general practitioners randomly selected from French telephone lists. Patients diagnosed with knee osteoarthritis (OA) were recruited when consulting an investigator for a symptom flare and were prescribed, or not, one of the SYSADOAs as per clinical judgment. Follow-up visits were as per routine medical practice in the 12 months following enrollment, with telephone interviews after 1 month and at 4-month intervals thereafter up to 24 months. Use of NSAIDs was recorded, as well as the dynamism of treatment exposure consisting of continuing the prescribed SYSADOA, switching, discontinuation or initiation of a SYSADOA. Patient exposure was expressed in 2-month time units, with any NSAID use as Yes/No binary outcome during each unit. Odds ratios [OR and 95% confidence interval (CI)] of NSAID use were calculated for periods of exposure to each SYSADOA, by multivariate logistic regression for an 80% power and 95% confidence to see a decrease of at least 15%.

Results: This report consists of the full data pertaining to crystalline glucosamine sulfate, while results of other SYSADOAs were summarized as available from the French Health Authority (HAS) website (www.has-sante.fr). Of 6451 patients in the PEGASus cohort, 315 patients received crystalline glucosamine sulfate, they were exposed for 481 2-month time units and had an incident use of NSAIDs of 18.7%. In the control cohort (9237 time units) NSAID incident use was 23.8%. Crystalline glucosamine sulfate significantly decreased the risk of NSAID consumption by up to 36% (OR = 0.64; 95% CI: 0.45–0.92) in the primary analysis foreseen by the protocol; OR was 0.74 (95% CI: 0.54–1.01), i.e. at the very limit of significance, in a sensitivity analysis accounting for an extension of the study and of the control cohort. None of the other SYSADOAs showed any hint of a decrease in the use of NSAIDs.

Conclusion: Crystalline glucosamine sulfate was the only SYSADOA that decreased the use of NSAIDs in this pharmaco-epidemiology study in patients with knee OA.

☆The PEGASus study was funded by the pharmaceutical companies marketing Symptomatic Slow-Acting Drugs in Osteoarthritis (SYSADOAs) in France, but it was conducted and analyzed by an independent research organization under the supervision of an independent scientific committee. In particular, Rottapharm S.A.R.L. (Paris, France) was the sponsor for the part of the study devoted to crystalline glucosamine sulfate, but the Rottapharm Group had no role in conducting, analyzing and reporting the study nor in the decision to publish the study or approval of the present manuscript for publication. The authors were employees of Rottapharm at the time of the study, but they left Rottapharm to join Rottapharm Biotech in 2014 and decided to publish the available data as independent scientists. Rottapharm Biotech is an independent company from the Rottapharm Group and does not market glucosamine sulfate or any other SYSADOA.

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Introduction

Drugs for osteoarthritis (OA) are developed with the aim of selectively controlling the symptoms of the disease (symptom-modifying drugs) and/or the disease progression in term of joint structure changes (structure-modifying or disease-modifying drugs). In particular, targeted symptom-modifying drugs in OA should be able to limit the consumption of unspecific symptomatic medications, including pure analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). There is in fact general concern regarding a possible overuse, especially of NSAIDs, given their poor safety profile on gastrointestinal, cardiovascular, renal, and other systems [1].

Consumption of rescue medications including analgesics and/or NSAIDs has been traditionally indicated as a possible ancillary outcome in clinical trials of new symptom-modifying agents, e.g., in the 1996 Osteoarthritis Research Society International (OARSI) guidelines [2]. However, such an outcome is difficult to assess in randomized controlled trials (RCTs), since it is prone to the patient's subjective response, with recourse to the rescue medication not necessarily linked to the severity of symptoms. In addition, recent evidence suggests that allowing concomitant symptomatic agents in RCTs of OA pain is associated with reduced assay sensitivity [3]. The new OARSI guidelines for conducting clinical trials in knee OA [4] actually no longer recommend rescue medication use as a reliable study outcome and ideally suggest to avoid the use of rescue analgesics in the trial to maximize the treatment effect. On the other hand, the recommendations acknowledge that this may adversely affect dropout and adherence rates, therefore suggesting to carefully standardize the recourse to rescue medications [4].

Symptomatic Slow Acting Drugs in OA (SYSADOAs), including glucosamine sulfate, chondroitin sulfate, diacerein, and avocado–soybean unsaponifiables (ASU), decrease OA symptoms with slow onset of action, and may delay the progression of joint structure changes along with symptom modification (disease-modifying effect), with different levels of evidence within the class [5]. Such medications are given orally for prolonged treatment courses and have the potential to decrease the use of drugs for rescue analgesia, including NSAIDs [6]. However, for the reasons described above, this effect was not well substantiated in clinical studies that so far produced only hints for such an effect [7–9]. In fact, the main concern of sponsors and investigators, in agreement with the recent OARSI recommendations [4], has always been rather to standardize the recourse to the rescue medication in order not to jeopardize the assay sensitivity. Such procedure deliberately resulted in non-significant differences with placebo in rescue analgesia use, e.g., in the long-term trials of chondroitin or glucosamine sulfate [10–12].

Pharmaco-epidemiology studies may be better suited than RCTs to detect an effect of SYSADOAs on the use of rescue or concomitant symptomatic drugs, given the real-life situation and the lack of constrictions imposed by RCTs. The Pharmaco-Epidemiology of GonArthroSis (PEGASus) study was designed to assess the impact of SYSADOAs on the use of NSAIDs.

Methods

Context and study design

The PEGASus study was requested and authorized by the French authorities for drug approval [Haute Autorité de Santé (HAS)] and reimbursement (Transparency Commission) to assess the impact of SYSADOAs on the use of NSAIDs in patients with knee OA, in order to further assess the efficacy of this drug class relative to this parameter and to substantiate the public health interest in the prevention of risks induced by NSAIDs. The study was funded by the pharmaceutical companies marketing SYSADOAs in France, but it was independently conducted and analyzed by an independent research organization, under the supervision of a Scientific Committee consisting of pharmacologists and two rheumatologists. The industry sponsors were involved as observers only, providing scientific input in the design of the study protocol and its amendments, as well as in the meetings of the Scientific Committee; they did not participate in the study performance, choice of investigators (whose list was not communicated to them), data collection, and statistical analysis.

The study protocol was approved by the relevant committees for the protection of patients in France [Comité Consultatif sur le traitement de l'information en matière de recherché dans le domaine de la santé (CCTIRS) in November 2009 and Commission Nationale de l'Informatique et des LIbertés (CNIL) in January 2010]. The protocol was amended with relevant approvals: in 2010 (prior to the study beginning) to finalize the design as a continuous cohort with "dynamic" exposure to prescribed treatments (see below); in 2011 (maximum treatment duration extended from 9 to 24 months); and 2012 (from enrollment of a fixed number of patients per site to a "competitive" enrollment, to facilitate patient recruitment).

PEGASus was designed as a cohort study of continuous recruitment of patients with dynamic exposure to the investigated treatments; "dynamism" constituted the registration of treatment with the prescribed SYSADOA as a function of treatment continuation, interruption and/or change in the SYSADOA prescribed. This dynamism was taken into account in the analysis, which was conducted by 2-month period of exposure (see below).

The following SYSADOAs (at approved dosages) were included in the study: glucosamine sulfate (as the original preparation of patented crystalline glucosamine sulfate), glucosamine hydrochloride, chondroitin sulfate, diacerein, and ASU. The methods and results of the PEGASus study are published on the website of the French Health Authority (HAS) (www.has-sante.fr). The present report consists of the full data for crystalline glucosamine sulfate, while the main results relevant to the other SYSADOAs are summarized from publicly available material (www.has-sante.fr).

Patient selection and investigators

Adult patients of both genders diagnosed with knee OA (and/or, to a lesser extent, hip OA for some of the investigated SYSADOAs) were recruited when consulting an investigator [rheumatologist or general practitioner (GP)] for a symptom flare of their OA. Major exclusions were patients receiving SYSADOAs for more than 3 months, or intra-articular hyaluronic acid in the last 3 months, or suffering from any other form of arthritis, tendinitis of the lower limbs, or radiculopathy. Patients were informed orally and in writing about the aims and procedures of the study and signed the informed consent form.

Investigators were randomly selected de novo from French telephone lists.

Study procedures

On the enrollment visit, patients were screened for eligibility according to the inclusion/exclusion criteria and the following were recorded: socio-demographic characteristics and anamnestic data, comorbidities, risk factors that may affect NSAID use, drugs used over the past 3 months, and the SYSADOA prescribed (if any). Follow-up visits occurred as required by standard medical practice in the 12 months following enrollment, with a telephone interview occurring after 1 month and at 4-month intervals (± 1 month)

thereafter, up to 24 months or earlier termination. In the interview or clinic visit, the following were recorded: adverse events, use of non-OA treatments and of treatments for OA, with start date and other details (dose, reason for prescription, regular use or as needed, and duration), including continuation of treatment with the prescribed SYSADOA (if any), prescription switch to another SYSADOA, discontinuation or start of treatment with a SYSADOA (if not prescribed at enrollment). Symptoms of OA were collected at enrollment and at follow-up visits/interviews by pain ordinal scale (0–10 score) and by the Lequesne index (0–24 scale) [13] in order to appropriately correct NSAID use data in the primary statistical analysis (see below).

Treatments

The present report describes in details the characteristics and the results of the cohort receiving oral crystalline glucosamine sulfate in the original formulation as sachets of powder for oral solution dosed as 1500 mg glucosamine sulfate (Osaflexan® in France, Dona® or Viartril-S® or other trademarks by the Rottapharm group, Monza, Italy elsewhere), and corresponding to 1178 mg of glucosamine. Crystalline glucosamine sulfate in this formulation is approved as a prescription drug throughout Europe and in over 60 countries of the world, and it is available as a branded and proprietary dietary supplement in the USA and other countries.

Other SYSADOAs evaluated in the PEGASus study were:

- Glucosamine hydrochloride two tablets, each corresponding to 625 mg (total 1250 mg) glucosamine, once daily
- Chondroitin sulfate 400 mg capsules or sachets, three times daily
- Diacerein 50 mg capsules, twice daily
- ASU 300 mg capsules, once daily.

The results for the primary endpoint (see below) for these other SYSADOAs were obtained from the publicly and freely available reports from the French Health Authority website (HAS) (www.has-sante.fr).

Statistical analysis

The primary analysis was conducted dividing the patient exposure in the study into time units, each time unit corresponding to a 2-month period. For each 2-month time unit in each patient (patient-time unit) the analysis considered whether the selected SYSADOA had been used (Yes/No) and whether there was any recourse to any NSAID (Yes/No, regardless of type of NSAID, dosage, treatment duration). The primary outcome was therefore represented by the risk [odds ratio (OR) and 95% confidence interval (CI)] of using an NSAID in patient-time units while receiving crystalline glucosamine sulfate or another SYSADOA, as compared with patient-time units when not receiving any SYSADOA. Such primary analysis was conducted by multivariate logistic regression according to a generalized estimating equation (GEE) model, adjusted for the following variables: gender, age (<60 years, 60–75 years, >75 years), pain score (<7 or ≥ 7), number of flares (0, ≤ 2, >2), Lequesne index ($<9/24$ or $\geq 9/24$), OA duration (≤ 1 year or >1 year), education level (lower or equal/higher than high school degree) recourse to physical treatments/orthoses/prosthesis (Yes/No), risk factors for potentially limiting NSAID use (history of cardiovascular or gastrointestinal disease, renal insufficiency, and hypersensitivity), presence of other treatments for OA including other SYSADOAs (Yes/No) or analgesics (Yes/No).

Socio-demographic and other variables were analyzed by descriptive statistics. The study was sized for each SYSADOA in order to have an 80% power and 95% confidence to see at least a 15% decrease in NSAID consumption risk. In particular, the crystalline glucosamine sulfate cohort was sized to detect an 18% decrease in NSAID consumption risk, with an hypothesized 27% rate of NSAID use in the control cohorts (consisting of 10,000 patient-time units, i.e., enough patients to provide 10,000 2-month periods), resulting in the requirement of 500 patient-time units on treatment with glucosamine sulfate.

The PEGASus study commenced in March 2010 for the SYSADOAs traditionally available on the French market (chondroitin sulfate, diacerein and ASU). Crystalline glucosamine sulfate and other glucosamines began commercialization in France during 2010 and their inclusion in the PEGASus study could start effectively in November 2010 at a reduced rate. As such, when the study was closed for chondroitin sulfate, diacerein, and ASU in October 2012, insufficient patients necessary to reach the calculated sample size had been achieved in the glucosamine cohorts. However, approximately 80% of the requested sample for crystalline glucosamine sulfate had been enrolled by October 2012 and the study Scientific Committee decided not to amend the protocol to modify the primary analysis which was forecasting the use of data from the control cohort (no SYSADOA) until October 2012 only. Nevertheless, it was decided to extend the follow-up of the original control cohort and to enroll a new control cohort from October 2012, to be used in sensitivity analyses. The PEGASus study was completed for glucosamines in April 2013. The primary analysis was conducted on the control cohort until October 2012, in agreement with the study protocol. A sensitivity analysis was performed using also the new control cohort and the follow-up period of the original control cohort after October 2012, until completion of the study in April 2013. Finally, an additional and partial analysis was included, modifying the main sensitivity in that it censored the original control cohort data generated after October 2012 and it was thus scarcely applicable as a sensitivity analysis.

The primary analysis foreseen by the protocol was also performed on ancillary outcomes, i.e., considering only patients who had been on glucosamine sulfate for at least 4 months, or taking into account a 2-month carryover effect after drug withdrawal; both are typical features of a SYSADOA [6].

Results

Participating physicians and patient population

The flowchart of physician selection and patient inclusion is depicted in Figure 1. A total of 38,014 GPs were randomly contacted, in addition to all private practice rheumatologists in France; 4052 physicians accepted to participate, and 745 physicians (642 GPs and 96 rheumatologists) included at least one patient in the study.

Overall, the PEGASus cohort recruited 6451 patients. Figure 2 reports the cumulative enrollment of patients throughout the study. Over 50%, i.e., 3725 patients completed the study interview at 12 months and 1154 at 24 months. A total of 315 patients received crystalline glucosamine sulfate during the study (Fig. 3), with an average follow-up of 10 months in the cohort. They contributed a total of 962 patient-months, i.e., 481 2-month time units, for the analysis of the primary endpoint.

Patients participating in the PEGASus cohort ($N = 6451$) had a mean age of 66 years, were overweight (mean BMI = 28), and 63% were women. Almost half of the patients had OA at multiple joints and lower limb OA was of moderate severity, with average 0–10 pain score of 5.6 points and severe handicap on the Lequesne index in 65% of patients. These data are described in Table 1,

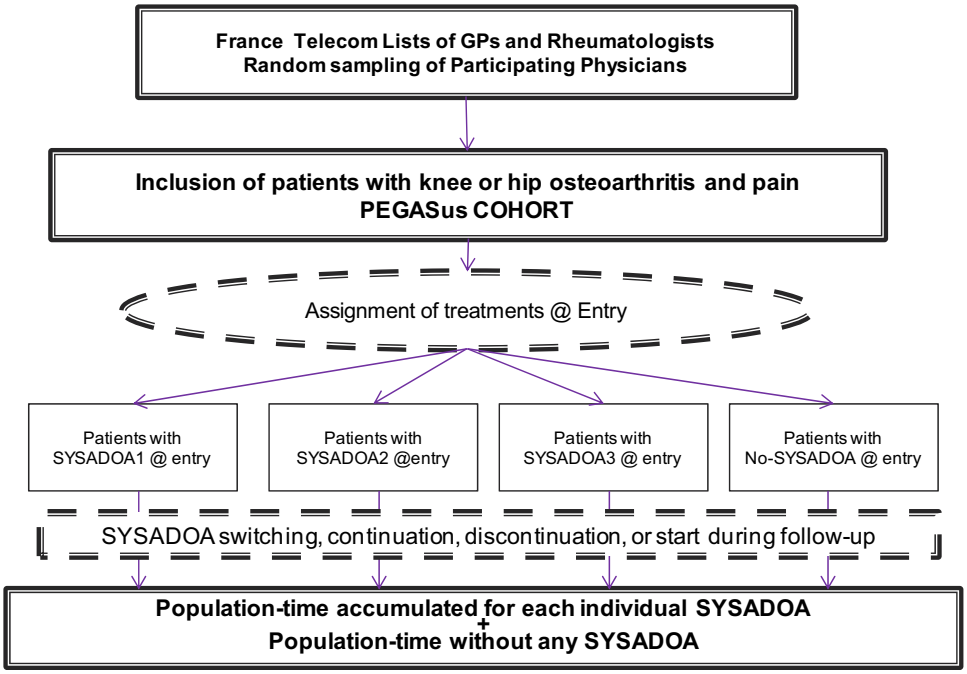

Fig. 1. Flowchart of physician selection and patient inclusion in the PEGASus study.

reporting patient characteristics in the completed PEGASus cohort excluding the 315 patients receiving crystalline glucosamine sulfate ($N = 6136$), in the crystalline glucosamine sulfate cohort ($N = 315$) and in the subcohort (within the 6136 patients) who received no SYSADOAs during the study and thus contributed to the majority of control patient-months and time units.

While there were no differences in the main demographic characteristics and disease severity, it appears that patients receiving crystalline glucosamine sulfate had a slightly shorter disease duration at enrollment and had a higher school education than the overall cohort, especially compared with patients never receiving a SYSADOA. Patients on glucosamine sulfate had also a history of slightly more allergies to NSAIDs, but also less risk factors such as cardiovascular, gastrointestinal, or urinary tract diseases.

Primary outcome for the crystalline glucosamine sulfate cohort

The 315 patients prescribed crystalline glucosamine sulfate contributed 962 patient-months to the primary analysis, corresponding to 481 2-month time units. Conversely, the control cohort time units

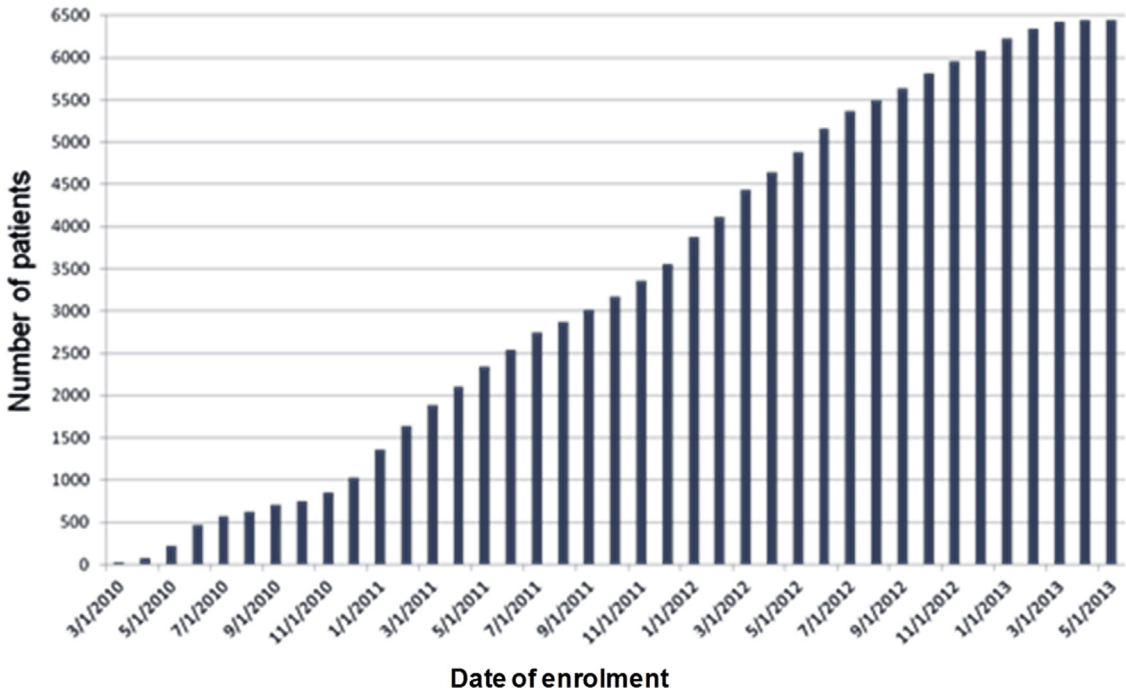

Fig. 2. Cumulative patient recruitment in the PEGASus complete cohort ($N = 6451$).

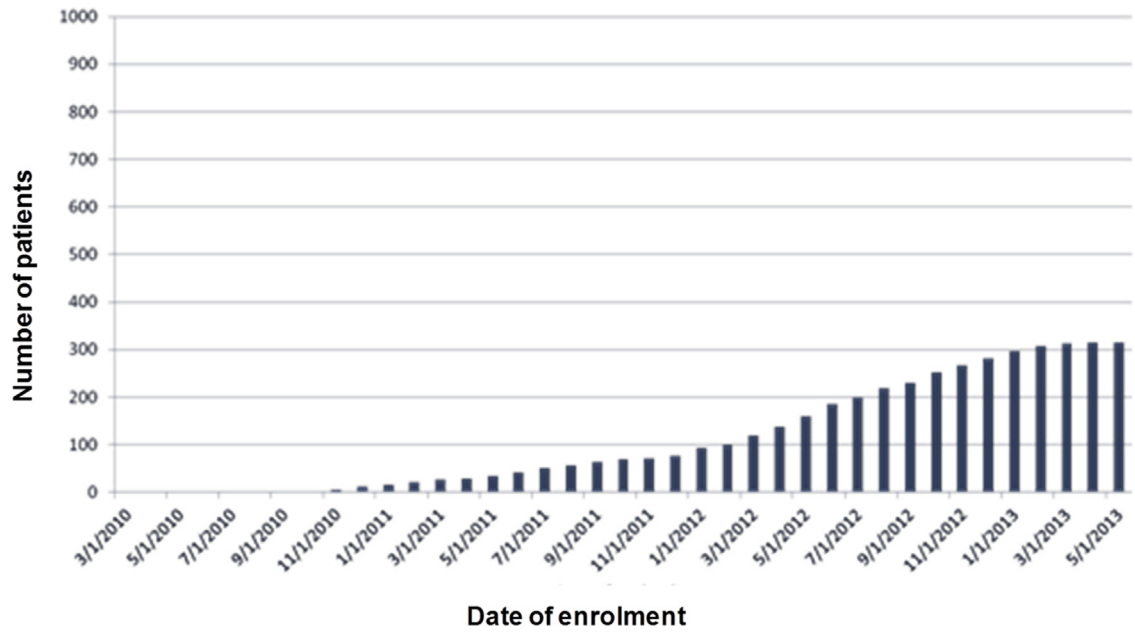

Fig. 3. Cumulative patient recruitment in the crystalline glucosamine sulfate cohort in the PEGASus study ($N = 315$).

without any use of SYSADOA consisted of 18,474 patient-months, i.e., 9237 time units. The results of the primary outcome are reported in Table 2.

In the control cohort there was an incident use of NSAIDs of 23.8% in the primary analysis, compared with 18.7% in the crystalline glucosamine sulfate cohort, i.e., a significant decrease in risk of 36% (OR = 0.64; 95% CI: 0.45–0.92). The sensitivity analysis accounting for the inclusion of new control patients and extending the follow-up of the original control cohort after October 2012, provided a similar result with an OR of 0.74 (95% CI: 0.54–1.01). The partial additional analysis provided a result in the same direction, but with wider confidence interval (data not shown).

In the primary analysis foreseen by the protocol, when only patients receiving glucosamine sulfate for more than 4 months were considered as a secondary outcome (420 patient-months) the decrease in risk was 48% and significant (OR = 0.52; 95% CI: 0.28–0.95), with an incident NSAID use of 16.2%.

Another secondary outcome consisted of the analysis performed including a 2-month carryover effect after crystalline glucosamine sulfate treatment withdrawal: the decrease in the risk of use of NSAIDs was significant (OR = 0.68; 95% CI: 0.47–0.96), with an incident NSAID use of 18.7%, although the analysis could be performed only in a small additional number of patients corresponding to 984 patient-months, i.e., 492 2-month time units.

Primary outcome for all other SYSADOAs cohorts

Figure 4 depicts the results for the primary outcome of the PEGASus study, as retrieved from the French Health Authority (HAS) website (www.has-sante.fr).

Table 1
Patient characteristics in the entire PEGASus cohort at enrollment ($N = 6451$), divided into patients who received no crystalline glucosamine sulfate and those who received crystalline glucosamine sulfate. The characteristics of the subcohort of patients who received no SYSADOA are also reported

	Patients who received no crystalline glucosamine sulfate ($N = 6136$)	Patients who received crystalline glucosamine sulfate ($N = 315$)	Patients who received no SYSADOA ($N = 1376$)
Age (years)	66.3 ± 12.0	64.4 ± 12.0	69.1 ± 11.9
Women, %	63.5	66.7	64.1
BMI	28.0 ± 5.0	27.4 ± 4.9	28.2 ± 5.1
OA duration (if reported), %			
< 1 year	25.7	25.5	21.7
1–5 years	41.8	43.9	40.2
> 5 years	31.0	27.1	37.7
Pain scale	5.6 ± 1.8	5.5 ± 1.8	5.5 ± 1.7
Lequesne index classification, %			
Mild/moderate (≤ 7 points)	35.2	35.4	35.3
Severe (≥ 8 points)	64.8	64.6	64.7
Physical therapy, %	11.8	11.1	10.9
Orthosis, %	11.9	8.0	15.3
Prosthesis, %	5.6	4.4	8.7
High school degree or higher, %	37.8	48.1	30.7
Allergy to NSAIDs, %	2.3	3.2	2.4
History of			
cardiovascular disease, %	57.6	49.5	63.6
gastrointestinal disease, %	23.4	20.4	25.0
genito-urinary disease, %	8.1	7.6	9.5
other OA joint localizations, %	42.6	45.7	42.9

Table 2
Risk (odds ratio and 95% CI) of NSAID use with crystalline glucosamine sulfate compared with controls in the PEGASus study: primary and sensitivity analysis

	Time units[a]	NSAID use (%)	Odds ratio (95% CI)
Primary analysis			
Control cohort	9237	23.8%	1
Crystalline glucosamine sulfate cohort	481	18.7%	0.64 (0.45–0.92)
Sensitivity analysis			
Control cohort	15,756	21.6%	1
Crystalline glucosamine sulfate cohort	481	18.7%	0.74 (0. 54–1.01)

[a] Each time unit corresponds to a two-month observation period.

It is evident that glucosamine hydrochloride had a very different effect compared with crystalline glucosamine sulfate, since it had no effect on NSAID use in the PEGASus cohort in the primary analysis (OR = 0.98; 95% CI: 0.81–1.19) or in the glucosamine cohort sensitivity analysis (OR = 1.09; 95% CI: 0.91–1.29). The same was true for all other SYSADOAs: neither chondroitin sulfate (OR = 0.94; 95% CI: 0.77–1.14), ASU (OR = 0.98; 95% CI: 0.82–1.17), nor diacerein (OR = 1.08; 95% CI: 0.87–1.33) decreased NSAID consumption in the primary analysis of the PEGASus study.

Discussion

Glucosamine sulfate, in the original formulation of prescription crystalline glucosamine sulfate 1500 mg once daily, decreased the use of NSAIDs in patients with knee OA in the Pharmaco-Epidemiology of GonArthroSis (PEGASus) study. Interestingly, glucosamine hydrochloride at a similar glucosamine daily dose was not able to attain a similar effect and other SYSADOAs, namely chondroitin sulfate, diacerein, and ASU at their usually prescribed doses, were also not able to decrease NSAID use in the PEGASus cohort.

SYSADOAs were developed as targeted medications for OA to be safer than, and at least as effective as, non-specific symptomatic medications such as pure analgesics and NSAIDs, able to control symptoms over long-term treatment courses with the added benefit of possible joint structure modification, and therefore disease modification [6]. In theory, SYSADOAs should also be able to decrease the consumption of NSAIDs for prolonged symptom control and/or for OA flares. This is a difficult outcome to assess in RCTs, given the often subjective NSAID use and the limitations imposed in rigorous studies by the standardization of rescue medications. Indeed, evidence for such an effect of SYSADOAs is limited in the scientific literature. In the 6-month GUIDE study of crystalline glucosamine sulfate vs. placebo and vs. paracetamol [7], the former decreased the proportion of patients using rescue NSAIDs compared with placebo and also reduced the number of days of use. However, this was only an additional analysis, and not the primary or secondary outcome in this rigorous pivotal trial with careful standardization of the rescue medication [7]. In another 6-month RCT, NSAID consumption was slightly lower with ASU than with placebo and fewer patients on ASU required NSAIDs [8]. Similarly, long-term users of chondroitin sulfate had lower use of NSAIDs or analgesics in a cross-sectional observational survey [9]; analogous evidence is scarce for diacerein. The PEGASus study was designed to confirm and expand such evidence with a pharmaco-epidemiology approach, which is probably more suitable than an RCT to assess this outcome given the real-life situation. Indeed, the PEGASus cohort was recruited from the standard clinical practice of 745 randomly selected GPs or rheumatologists, from their patients consulting for a lower limb painful OA flare. Patients (and physicians) could modify their treatment as in real-life, e.g., stop the prescribed SYSADOA, shift to another SYSADOA, continue or start one or another for a follow-up of up to 24 months, with scheduled interviews to record the main treatment data and risk factors that may affect them. All information was taken into account in the statistical analysis, that was organized in 2-month time units with a binary outcome (NSAID use: Yes/No).

Glucosamine sulfate given as the patented crystalline glucosamine sulfate formulation [14] decreased the risk of using NSAIDs by up to 36%. The study had an 80% power to see an 18% decrease in NSAID consumption risk with a hypothesized 27% rate of NSAID use in the control cohort and 500 time units on glucosamine sulfate. Given the time constraints imposed by the French Health Authority to receive the study data, there were 481 time units for the 315 patients in the glucosamine sulfate cohort, close to the postulated 500 time units. Despite the slightly lower than hypothesized recourse to NSAIDs in the control cohort,

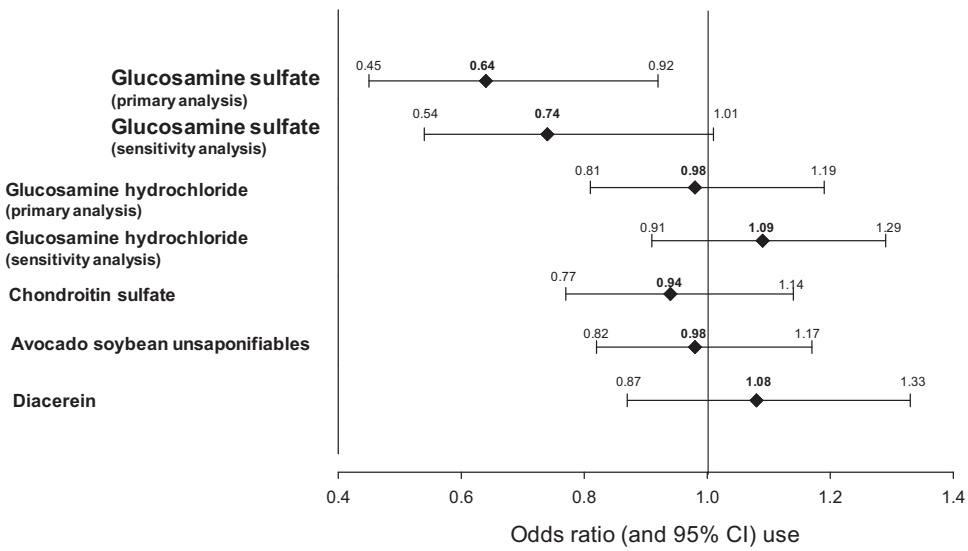

Fig. 4. Odds ratio (with 95% CI) of NSAID use with SYSADOAs in the PEGASus study.

i.e., 23.8%, the 36% decrease with glucosamine sulfate was statistically significant and clinically relevant in the primary analysis foreseen by the protocol. Since the glucosamine cohorts entered the PEGASus study later than other SYSADOAs and the stipulated number of patients had not been reached by study end, it was necessary to prolong the observation period of the original control cohort. An additional control cohort was also started and used in a sensitivity analysis that included all reference time in the different control cohorts. The results were in the same direction, with a decrease in risk of 26% that was at the very limit of statistical significance (upper 95% confidence limit: 1.01) probably because of the further slight decrease in NSAID use, 21.6%, in the prolonged control cohort. On the other hand, the significant results of the protocol primary analysis are reliable, because approximately 80% of glucosamine sulfate patients had already been recruited when the original control cohort foreseen by the protocol primary analysis was extended, and a new control cohort started with the aim of performing the sensitivity analysis.

In secondary analyses, the decrease in risk was even higher (52%) when glucosamine sulfate was used for longer than 4 months. The effect was still significant when a 2-month carry-over effect, a typical feature of SYSADOAs [6], was included in the analysis.

This present report is devoted to the full results obtained with crystalline glucosamine sulfate. Reporting the detailed data for each SYSADOA tested in the PEGASus study falls outside the scope of this article. Results for all other compounds tested are publicly accessible on the French Health Authority (HAS) website (www.has-sante.fr) and the data of the primary analysis are summarized here. In this respect, it is first of all interesting to note that glucosamine hydrochloride was not able to decrease NSAID consumption. Glucosamine hydrochloride is widely used as a dietary supplement as it is unpatented, readily available, easy to handle, inexpensive, and, unfortunately, it has been approved by some health authorities as an over-the-counter (OTC) medication or a generic of crystalline glucosamine sulfate. Actually, in our opinion this is completely inappropriate, since glucosamine hydrochloride has never been shown to be effective in knee OA, which is quite the opposite for glucosamine sulfate, as nicely described in a meta-analysis by OARSI within one of its treatment guidelines documents [15]. Glucosamine hydrochloride was not found effective even in selected large and rigorous clinical trials such as the NIH-sponsored GAIT (Glucosamine/chondroitin Arthritis Intervention Trial) study [16]. Indeed, glucosamine hydrochloride has a different pharmacokinetic profile than crystalline glucosamine sulfate, resulting in a 50–75% decrease in bioavailability when given at standard doses and formulations [17]. Therefore, the data from PEGASus support what is already known from the literature.

It is more difficult to interpret the lack of effect in decreasing NSAID consumption found with other SYSADOAs. The recent European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm recommendations for knee OA [5] advise that only the prescription formulations of glucosamine sulfate (i.e., the patented crystalline glucosamine sulfate described here) or chondroitin sulfate should be used in the first step of treatment as long-term pharmacological background, since the evidence is scarce for other SYSADOAs such as ASU or diacerein. More data are therefore needed for chondroitin sulfate in order to attain a similar level of evidence shown in PEGASus for crystalline glucosamine sulfate with respect to a sparing effect on rescue NSAID use.

As already discussed in the reports of crystalline glucosamine sulfate pivotal trials [7,11,12], it is unlikely that the data obtained here can be transferred to OTCs or generics claiming the use of other supposed glucosamine sulfate formulations. These formulations may indeed be unstable and lose most of their label content in glucosamine [18], since they are not using the same patented method of stabilization of crystalline glucosamine sulfate [14] and may even have a different pharmacokinetic and pharmacological profile [17]. It is well known that there are no favorable trials of glucosamine sulfate other than those with crystalline glucosamine sulfate. In fact, the latest edition of the glucosamine Cochrane Review failed to show any efficacy on pain of these other formulations (including glucosamine hydrochloride) in high-quality trials [19], while the efficacy is statistically significant when the three high-quality pivotal trials of crystalline glucosamine sulfate are pooled [19] and the effect size is clinically relevant as also shown in other recent meta-analyses [20,21]. The prescription formulation of crystalline glucosamine sulfate is recommended by the European guidelines [22] and in the recent ESCEO algorithm recommendations [5], while glucosamine's role is described as uncertain in the American College of Rheumatology (ACR) or OARSI guidelines [23,24], given the lack of prescription products in the US in the former [23] and the authors' decision not to differentiate between the different glucosamine formulations in the latter [24], contrary to previous OARSI guideline documents [15].

Conclusion

The patented formulation of prescription crystalline glucosamine sulfate was the only SYSADOA able to decrease rescue NSAID use in the PEGASus study. These data further confirm the unique efficacy of this crystalline glucosamine sulfate formulation in the management of knee OA.

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