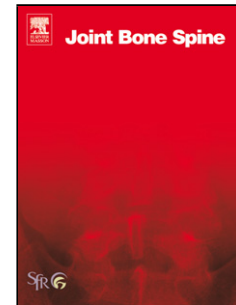# Accepted Manuscript

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Statin use and knee osteoarthritis progression: Results from a post-hoc analysis of the SEKOIA trial

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Abstract

Objective: Epidemiological and experimental studies have suggested that lipid disorders might be involved in the pathophysiology of knee osteoarthritis (OA). Studies assessing the effect of statins on knee OA progression have shown conflicting results. We investigated the impact of statin use on radiological progression in patients with radiological and symptomatic knee OA.

Methods: 336 patients from the placebo arm of SEKOIA trial completed the 3-year follow-up and were included in this post-hoc analysis. Statin use was recorded at baseline interview. Minimal medial tibiofemoral joint space was measured on plain radiographs by an automated method at baseline and then annually. Radiologic progression was defined as joint space narrowing ≥ 0.5 mm over 3 years.

Results: Overall, 71 patients were statin users (21.1%). They had a higher BMI (31.1 ± 5.3 vs. 29.3 ± 5.2 kg/m², p = 0.008), a higher sum of metabolic factors (≥3 factors: 43.7% vs 7.2%; p for trend < 0.001) and a higher rate of radiological progression (49.3% vs. 32.1%, p = 0.007) as compared to statin non-users. The significant association between radiological progression and statin use was independent of age, gender, WOMAC global score, disease duration, baseline joint space width, hypertension, type 2 diabetes, obesity (BMI > 30 kg/m^2) and cardiovascular diseases [relative risk 1.49 (95% CI 1.10–2.02), p = 0.010].

Conclusion: Among patients with knee OA, statin use was associated with radiological worsening over 3 years, regardless of other potential confounding factors (obesity, type 2 diabetes, hypertension, disease duration, symptom intensity and radiological severity).

Keywords: knee osteoarthritis, radiological progression, statin, dyslipidemia

Introduction

Knee osteoarthritis (OA), the most common joint disease [1] is a complex pathology with several etiologies [2]. Two main pathophysiological mechanisms are usually distinguished: a local "mechanical" one, related to increased load on the joint compartment, and a general "systemic" one, related to the release of proinflammatory mediators (adipokines, cytokines, etc.) from several organs such as adipose tissue [2,3]. OA associated to metabolic disorders is an example of systemic factor involvement. Several studies highlighted the cumulative impact of metabolic disorders (abdominal obesity, hypertension, diabetes, dyslipidemia) on the onset or progression of knee OA [4-7]. Each metabolic disorder was also studied as an individual potential risk factor for knee OA, and several studies focused on dyslipidemia [4-8]. Two studies found a significant association between lipid disorders and early or late radiological aspects of knee OA [5,8]. Davies-Tuck *et al.* showed that serum cholesterol and triglyceride levels were associated with the incidence of bone marrow lesions over 2 years (Odds Ratio [OR] 1.84, p = 0.048) and 8.4, p = 0.01, respectively) in a population of asymptomatic middle-aged women [8] while Karvonen-Gutierrez *et al.* noted that a 5 mg/dL higher LDL-c was associated with 5-6% greater odds of osteophytes-defined radiographic knee OA in men [5]. From these findings was born the hypothesis that dyslipidemia treatments (statins and fibrates) might have a beneficial effect on radiological progression.

The effect of statins on knee OA progression was recently assessed by few studies with a comparable methodology. However, they found conflicting results. Clockaerts *et al.* [9] showed that statin use reduced radiological progression (OR = 0.43, p=0.01), whereas Riddle *et al.* [10] did not show any impact of statin use. Thus, the effect of statin use on knee OA progression remains an unresolved issue. A weakness of the previous studies was the definition of radiological progression based on worsening in Kellgren and Lawrence (KL)

score [11], which is weakly sensitive to small changes [12]. A more precise approach to monitoring radiological progression can be obtained by strict radiographic measurement of joint space width (JSW), still regarded as the gold standard in chondroprotective trials [13].

SEKOIA, a randomised, double blind, placebo-controlled phase 3 trial that assessed the impact of strontium ranelate on knee OA, provided a unique opportunity to study potential predictive factors of radiological progression based on an accurate semi-automatic measurement of JSW in patients with symptomatic knee OA [14]. The main purpose of this study was to assess the involvement of statin use in knee OA radiological progression.

Methods

Characteristics of the SEKOIA study

SEKOIA was a randomised, double blind, placebo-controlled phase 3 trial of outpatients with symptomatic knee OA performed in 98 centres in 18 countries. This 3-year study compared the effectiveness of strontium ranelate (1 or 2 g/day) and placebo on knee OA radiological progression and symptoms [14]. Data for all patients in the placebo arm with 3-year follow-up data were included in this post-hoc analysis.

Study design and patients

All details of study design and inclusion criteria were described previously [14,15]. Briefly, the study included Caucasian ambulatory men and women $\geq$ 50 years old with symptomatic and radiographic evidence of knee OA according to American College of Rheumatology criteria [16] and the KL scale [11], respectively. Radiological inclusion criteria included OA features defined by KL grade 2 [definite osteophytes and possible joint space narrowing (JSN)] or grade 3 (moderate multiple osteophytes, definite JSN, some sclerosis, and possible deformity of bone ends) and JSW of the medial tibiofemoral compartment of 2.5

to 5 mm. If both knees fulfilled the selection criteria, the target knee was the most painful; if both knees were equally painful, the target knee was the one with the highest KL grade and/or the lowest JSW; and if both knees had the same radiographic score, the target knee was determined by the investigator's judgement. Exclusion criteria were knee prosthesis, recent intra-articular injection (notably glucocorticoids < 3 months previously or hyaluronic acid < 6 months previously), clinical deformities, secondary knee OA, previous treatments for cartilage or bone metabolism (e.g., oral or intravenous bisphosphonates < 1 year previously, teriparatide or raloxifene < 7 days before selection, and oral glucosamine ≥ 1500 mg/day and chondroitin sulphate < 3 months previously), and a history or a high risk of venous thromboembolism (contraindication for strontium ranelate).

Baseline examination

Medical history was recorded for each patient at baseline. Height and weight were measured and BMI was calculated; obesity was considered ≥ 30 kg/m^2. The presence or absence of the following metabolic factors: diabetes mellitus, hypertension, dyslipidemia and obesity was noted. Moreover, a history of ischemic disease such as ischemic heart disease and peripheral arterial vascular disease was recorded. Smoking status and alcohol consumption were also noted. Statin users were defined as patients reporting intake of one of the following statins at baseline: simvastatin, atorvastatin, atorvastatin calcium, fluvastatin sodium, lovastatin, nyastatin, pravastatin, pravastatin sodium, rosuvastatin, and rosuvastatin calcium.

Other investigations involved the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and global knee pain [visual analogue scale (VAS)] at inclusion. WOMAC evaluates OA health status and outcomes with 24 questions [17] summarized as a total score and pain, stiffness and physical function subscores. For each question, we used a 100-mm scale, with a maximal score of 2400 mm for the total score, 500

mm for pain, 200 mm for stiffness, and 1700 mm for physical function, lower scores indicating better status.

Radiological assessment

Posteroanterior knee radiographs of both knees were taken at inclusion and then annually on the target knee alone by use of a standardised technique [18]. A reproducible knee fixed flexion (20°) was achieved by using a SynaFlexer positioning frame (SynarcInc, San Francisco, CA, USA). The X-ray beam was tilted at a fixed angle of 10° to optimise alignment of the medial tibial plateau. Quality control (SynarcInc, Hamburg) included specifications for image acquisition and collection (e.g., depiction, positioning and beam angle), regular training for radiology technicians, determination of radiological eligibility, and onsite and centralised digitisation and quality control of radiographs [15].

Minimal JSW (mm) at the medial tibiofemoral compartment was measured by a standardised computer-assisted method [15,19]. Briefly, magnification was determined (radio-opaque ruler) and a region of interest was delimited by a horizontal tangent to the inferior edges of each femoral condyle and 2 perpendiculars to the condylar margins. Within an area defined automatically by 2 parallel lines 15 mm apart (one 10 mm from the condyle line), the observer delineated the tibial and femoral bone margins to depict a polygon; JSW was the diameter of the smallest circle (automatically calculated) in this polygon.

All radiographs were measured centrally (INSERM UMR 1033, Lyon, France) by a single reader blinded to treatment allocation and patient identity. Each blinded post-baseline image was measured in comparison with the inclusion image to optimise reproducibility and sensitivity [20-22]. Intrareader reproducibility was evaluated yearly with 70 knee radiographs unlinked to the study; reproducibility was excellent (intraclass correlation coefficient for JSW > 0.90) [19]. Radiological progression was defined as JSN ≥ 0.5 mm over 3 years [23,24].

Statistical Analysis

Baseline continuous characteristics of participants were checked for normality and summarized by means and SD, and counts and percentages were used for binary and categorical characteristics. For the univariate analysis, clinical and radiological characteristics of statin users and non-users were compared by Student *t* test, chi-square test, Mann Whitney U test or Fisher exact test as appropriate. We used multivariate logistic regression analysis with progressive adjustment. The 3 successive models used to assess the specific involvement of statin use in knee OA progression were as follows: Model 1, adjustment for age and gender; Model 2, adjustment for age, gender, baseline WOMAC global score, disease duration and baseline JSW; Model 3, adjustment for age, gender, baseline WOMAC global score, disease duration and baseline JSW, hypertension, type 2 diabetes, obesity (BMI > 30 kg/m^2) and cardiovascular diseases. P < 0.05 was considered statistically significant. All analyses involved use of Stata 13 (StataCorp, College Station, TX).

Results

Demographic characteristics

In total, 559 patients were randomly allocated to the placebo group of the SEKOIA trial; 336 patients completed the 3-year follow-up and were included in this post-hoc analysis. Seventy-one patients were statin users (21.1%) (Table 1). Except 1 patient, all statin users had dyslipidemia. In contrast, 28 of the 98 dyslipidemic patients were not treated by statins. BMI was higher for users than non-users. Prevalence of type 2 diabetes and hypertension and sum of metabolic factors were higher in statin users. Prevalence of ischemic heart diseases was also higher in statin users. The groups did not differ in smoking and alcohol consumption, disease duration, knee pain at baseline and WOMAC scores at baseline. Similarly, no

statistical differences were found regarding JSW and KL grade at baseline.

Impact of statin use on knee OA worsening

Rate of radiological progression was greater for statin users than non-users (p<0.01). JSN over the study duration was higher but not significantly (Table 1).

On univariate analysis, risk of radiological progression was greater for statin users than non-users (p<0.01) (Table 2). After adjustment for age, gender, baseline WOMAC global score, disease duration, baseline joint space width, hypertension, type 2 diabetes, obesity (BMI > 30 kg/m^2) and cardiovascular diseases, radiological progression over study duration remained significantly associated with statin use [RR =1.49 (1.10-2.02), p = 0.010]. No statistically significant association was found between dyslipidemia and radiological progression [univariate model: RR=1.26 (95% CI 0.94-1.69)].

Discussion

Our study is the first to show in a population of symptomatic knee OA that statin users were more likely "radiological progressors", regardless of other potential confounding factors (obesity, type 2 diabetes, hypertension, disease duration, symptom intensity and radiological severity).

Our findings are consistent with those published by Beatties *et al.* who showed that statin use was associated with an increase risk of developing incident hip OA in elderly women [25]. However, previous studies investigating the effect of statins in patients with knee OA found opposite results. Valdes *et al.* [26] and Riddle *et al.* [10] did not show any impact of statin use on knee OA prevalence or progression, respectively, whereas Clockaerts *et al.* found a protective effect of statins on radiological progression [9]. Nevertheless, each study had a specific design with some limitations. Indeed, these were a cross-sectional case–

control study [26] or longitudinal cohort study [10]. Neither benefited from the methodological rigor of the SEKOIA study, which was an international, multicentre, controlled, randomized trial with precise data collection [14,15]. Most of the patients in the Clockaerts *et al.* study [9] and a significant proportion in the Riddle *et al.* study [10] had no knee OA at baseline whereas the SEKOIA study included a homogeneous population of symptomatic and radiological knee OA. Moreover, the SEKOIA trial offers the benefit of accurate and sensitive measurement of radiological progression performed by a standardised computer-assisted method. Inversely, previous studies assessed radiological progression by the KL score, which is known to be not sensitive to change. Thus, progression rates over 6 years for statin users and non-users were particularly low in the Clockaerts *et al.* study (3.0% and 7.3%, respectively) as was the increase in KL grade over 4 years in the Riddle *et al.* cohort. Finally, Clokaerts *et al.* [9] included subjects with a mean BMI that was significantly lower than that usually reported (approximately 26.3 vs 30.3 kg/m^2 in a French cohort [27] and 30.4 kg/m^2 in a Dutch cohort [28]). Thus, we may assume that the population included in this study was not a population at risk to develop knee OA. In the SEKOIA trial, the mean BMI was 29.4 kg/m^2 [14].

Several in vivo studies found that oral use or intra-articular injections of statins inhibited cartilage degradation in rabbit or murine OA models [29-33], and in vitro studies confirmed that statins decreased the gene expression or secretion of inflammatory and catabolic factors by animal or human OA chondrocytes [29,32-36]. Conversely, one study, based on a spontaneous OA murine model (STR/ORT), did not find any impact of statin use on systemic inflammation, cartilage degradation or subchondral bone thickness [37].

Given the in vitro and in vivo benefit of statins observed from most of the aforementioned studies, how can we explain our unexpected results?

A major issue raised from our findings is the causality between statins use and knee

OA worsening. Systemic bias or a reverse causation cannot be ruled out in our study, as was previously reported in analyses that consider statin use and colorectal cancer [38] or dementia risk [39]. Confusion bias could also be involved. Indeed, recent studies demonstrated that statins increased the risk of type 2 diabetes in a dose-dependent manner [40], which is a known risk factor of knee OA progression [41,42]. However, as we statistically adjusted on diabetes status, its impact in our study seems unlikely. Statins are also known to cause muscle pain and weakness [43], also clearly associated with radiographic progression of knee OA [44]. As this variable was not assessed in SEKOIA study, we may hypothesize that statins could lead to knee OA progression through this side effect.

Otherwise, as 70 of 71 statin users had dyslipidemia, we may hypothesize that statin use is an equivalent of a dyslipidemia condition such as anti-hypertensive and anti-diabetic treatments for hypertension and diabetes, respectively. Thus, according to our results, dyslipidemia could be considered a predictive factor for greater radiological progression regardless of the presence of other metabolic factors. This hypothesis could also explain the conflicting results with Riddle *et al.* and Clockaerts *et al.* studies. Indeed, they differ from the SEKOIA trial in that patients receiving with statins at baseline were excluded in these studies, so subjects with the most severe dyslipidemia may not have been represented [9,10].

The potential role of dyslipidemia is supported by previous observational studies [5-8] and several experimental studies highlighting a harmful effect of various lipid mediators (cholesterol, free fatty acids) on human or murine cartilage explants, chondrocytes and synoviocytes [33,45-48]. Nevertheless, some other epidemiological studies found conflicting results, showing no link between dyslipidemia and OA [4,6,7]. In the SEKOIA trial, we recently reported the lack of an association between dyslipidemia and annual JSN in the placebo group [41]. Moreover, in this new post-hoc analysis including only the completers of SEKOIA trial, no significant association was found between dyslipidemia and radiological

progression after 3 years. This could be an argument against the specific implication of dyslipidemia in OA progression. However, 98 completers from the SEKOIA placebo group reported dyslipidemia at baseline whereas only 70 received statin therapy. We may assume that the 28 dyslipidemic subjects untreated with statin (28.6%) did not actually have dyslipidemia or had less severe disease, which could explain this result. On the other hand, we can not exclude that some of SEKOIA patients used statins as a secondary prevention treatment after vascular disease even though they had no significant dyslipidemia. We may also suppose that some statin users had a better-controlled disease with lower cholesterol or triglyceride levels.

As distinguishing the respective impact of statin consumption from dyslipidemia in radiological progression of knee OA is difficult, a randomised controlled trial including patients with symptomatic knee OA will be performed to assess the effect of statin use on structural and clinical progression after a 2-year follow-up [49]. Given its interesting design, with the exclusion of patients with metabolic disorders (dyslipidemia, diabetes, cardiovascular disorders), the specific effect of statins on OA progression will not be biased.

Our study has some limitations. First of all, SEKOIA study did not plan to collect daily dose and duration of statin neither at baseline nor during the 3 years of follow-up. Consequently, we were not able to analyse the potential cumulative impact of statin use on radiological progression. In addition, cholesterol or triglycerides levels were not available, so patients could not be classified by dyslipidemia severity.

In conclusion, we observed a negative impact of statin use on radiological progression as measured by a standardised computer-assisted method after 3 years of follow-up independently of other potential confounding factors (obesity, type 2 diabetes, hypertension, disease duration, symptom intensity and radiological severity). We cannot exclude that dyslipidemia, severe enough to justify statin use, might be the underlying factor explaining

this association.

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Table 1. Demographic and radiological data for statin users and non-users in the placebo arm of the SEKOIA trial at baseline and the end of study (36 months) (n=336).

	Statin users (n=71; 21.1%)	Statin non-users (n=265; 78.9%)	p-value
Sex (female)	46 (64.8%)	188 (70.9%)	NS
Age (years)	64.0 ± 6.9	62.3 ± 7.3	NS
Weight (kg)	84.6 ± 16.4	79.8 ± 15.8	**p<0.05**
Height (cm)	164.7 ± 9.6	165.0 ± 9.3	NS
BMI (kg/m^2)	31.1 ± 5.3	29.3 ± 5.2	**p<0.01**
Obesity (BMI >30 kg/m^2)	39 (54.9%)	101 (41.1%)	**p<0.05**
Diabetes type 2	8 (11.3%)	10 (3.8%)	**p<0.05**
Hypertension	49 (69.0%)	106 (40.0%)	**p<0.001**
Sum of metabolic factors §			**p<0.001**
0	0 (0.0%)	97 (36.6%)	
1	12 (16.9%)	95 (35.8%)	
2	28 (39.4%)	54 (20.4%)	
3	23 (32.4%)	17 (6.4%)	
4	8 (11.3%)	2 (0.8%)	
Ischemic heart diseases	14 (19.7%)	23 (8.7%)	**p<0.01**
Peripheral arterial disease	0 (0.0%)	2 (0.8%)	NS
Smoking			NS
No	44 (62%)	179 (67.5%)	
Past or current user	27 (38%)	86 (32.5%)	
Alcohol consumption			NS
No	32 (45.1%)	134 (50.6%)	
Past or current user	39 (54.9%)	131 (49.4%)	
Knee OA duration (months)	86.8 ± 79.9	73.3 ± 75.2	NS
Baseline knee pain VAS (0-100 mm)	56.2 ± 22.3	53.9 ± 23.4	NS
Baseline WOMAC score †			
Total (/2400 mm)	1071.6 ± 481.9	959.8 ± 511.6	NS
Pain (/500 mm)	223.9 ± 103.2	202.2 ± 108.5	NS
Stiffness (/200 mm)	97.5 ± 434.8	86.8 ± 50.0	NS
Physical function (/1700mm)	734.6 ± 361.0	671.5 ± 382.7	NS
Baseline KL grade			NS
Grade 2	39 (54.9%)	177 (66.8%)	
Grade 3	32 (45.1%)	88 (33.2%)	
Baseline knee JSW (mm)	3.47 ± 0.84	3.57 ± 0.84	NS
Knee JSW at the end of study (mm)	2.93 ± 1.13	3.19 ± 1.01	NS
Knee JSN over the study	0.54 ± 0.66	0.38 ± 0.61	NS
Radiological progression over the study ♮	35 (49.3%)	85 (32.1%)	**p<0.01**

Data are number of patients (%) or mean ± SD. NS, non significant. BMI, body mass index. VAS, visual analogue scale. WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. KL, Kellgren and Lawrence. JSW, joint space width. JSN, joint space narrowing. § Metabolic factors were : obesity, diabetes type 2, hypertension and dyslipidemia. † Each WOMAC item is measured on a 100-mm scale. ♮ Radiological progression was defined as JSN ≥ 0.5 mm over 3 years. Binary or categorical data were compared by chi-square test or Fisher exact test and continuous data with Student t test or Mann Whitney U test.

Table 2. Univariate and multivariate analysis of relative risk of radiological progression for statin users and non-users in the placebo arm of the SEKOIA trial (36 months).

	Univariate analysis	Multivariate analysis		
		Model 1	Model 2	Model 3
Statin non-users	1	1	1	1
Statin users	1.54 [1.15-2.06]	1.51 [1.13-2.03]	1.53 [1.14-2.06]	1.49 [1.10-2.02]
P-value	**p<0.01**	**p<0.01**	**p<0.01**	**p=0.01**

Data are relative risk [95% CI]

Model 1: Adjustment for age and gender

Model 2: Adjustment for age, gender, baseline WOMAC global score, disease duration and baseline joint space width

Model 3: Adjustment for age, gender, baseline WOMAC global score, disease duration, baseline joint space width, hypertension, type 2 diabetes, obesity (BMI>30 kg/m^2,) and cardiovascular disease