Risk factors predictive of joint replacement in a 2-year multicentre clinical trial in knee osteoarthritis using MRI: results from over 6 years of observation

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ABSTRACT

Objective To identify predictive factors for total knee replacement (TKR) using data from MRI of knee osteoarthritis patients in a phase III multicentre disease-modifying osteoarthritis drug (DMOAD) study.

Methods Knee osteoarthritis patients from a 2-year clinical trial evaluating licofelone versus naproxen were investigated for the incidence of TKR of the study knee. Patients (n=161) who completed the study according to protocol were selected. Incidence of TKR was assessed blindly to the treatment following telephone interviews (n=123).

Results 18 TKR (14.6%) were performed in 4–7 years following enrolment in the original study. More TKR were performed within the naproxen than the licofelone group (61% vs 39%, p=0.232). Baseline score of bone marrow lesions (BML) in the medial compartment (p=0.0001), medial joint space width (JSW) as assessed by standardised radiographs (p=0.0008), presence of severe medial meniscal tear (p=0.004), medial meniscal extrusion (p=0.013), and C-reactive protein level (p=0.049) were strong predictors of TKR. Changes at the end of the study also yielded strong predictors: change in cartilage volume of the medial compartment (p=0.005) and of the global knee (p=0.034), reduction in the JSW of greater than 7% (p=0.009), and WOMAC pain (p=0.009) and function (p=0.023) scores. Multivariate analysis showed that baseline severe medial meniscal tear (p=0.023) and presence of medial BML (p=0.025) were the strongest independent long-term predictors of TKR.

Conclusion This study shows that in the context of osteoarthritis trials, clinical data and structural changes identified by MRI allow prediction of a 'hard' outcome such as TKR. The findings support the usefulness and predictive value of MRI in defining study outcome in DMOAD trials.

Osteoarthritis treatment remains largely symptomatic.[1 2] Although studies using x-rays, which is still the most common technology used[3] and is recommended by regulatory agencies for phase II and III disease-modifying osteoarthritis drug (DMOAD) trials, have shown that some drugs may have disease (structure) modifying effects in knee osteoarthritis patients,[4–8] in recent years, a number of studies have used MRI technology to assess the structural changes in knee osteoarthritis.[3 9–15] The latter has been demonstrated to be a sensitive and reliable tool for such assessment over time, and enables the identification of risk factors associated with cartilage volume loss including meniscal tear/extrusion and subchondral bone marrow lesions (BML).[10–12 14 16 17] Using this technology, we recently reported the results of a phase III trial with respect to the DMOAD effects of licofelone, a pyrrolizine derivative that acts as a competitive inhibitor of both 5-lipoxygenase and cyclooxygenase, in knee osteoarthritis patients.[18] This and a recent study evaluating the effects of celecoxib[19] provided a strong rationale for the use of quantitative MRI in knee osteoarthritis DMOAD studies. These MRI trials proved to be instrumental in providing reliable and sensitive information about the effects of the drugs on cartilage loss, in addition to providing new insight into the roles played by risk factors, such as meniscal lesions, in patient response to treatment.

The guidelines from the European and US regulatory agencies require that joint structure modification also translates into a significant clinical benefit for the patient before allowing the claim of DMOAD.[20 21] The prevention of patient disability and prevention of the need for joint replacement have been suggested as possible clinically relevant outcomes.[22] Others have used joint replacement as an outcome of which baseline variables may be predictive in the long term[23–26] or total knee replacement (TKR) on post-hoc analyses of previous therapeutic interventions.[27]

We thus elected to use the data from our recently published study[18] to conduct a post-hoc analysis addressing the important question: can the occurrence of TKR be predicted using clinical and MRI data from long-term follow-up of knee osteoarthritis patients in a randomised clinical trial?

PATIENTS AND METHODS

Patient selection and time to TKR procedure

Data from the original recently published clinical trial[18] were selected from the patients who completed the study according to protocol (ATP). It was felt by the investigators that full adherence to the study regimen was necessary to yield any significant conclusion regarding a later need for TKR. In this clinical trial,[18] patients with primary symptomatic knee osteoarthritis of the medial tibiofemoral compartment were randomly assigned to receive either therapeutic dosages of licofelone (200 mg twice a day) or naproxen (500 mg twice a day) for 2 years. The enrolment period of the clinical trial started in December 2001 and the last patient entered in the study completed the 2-year trial in December 2007.

A phone interview was conducted between November 2009 and January 2010 with 123 patients from six out of the 10 collaborative centres from the original ATP cohort of 161 subjects. Twenty patients were unreachable for various reasons. These post-hoc phone interviews were approved by the local ethics committees. Assessors from the centres, blinded to treatment, asked the patients the following specific questions: Did you have a total knee replacement? If so, which knee (left or right or both)? And if so, on which date was the surgery performed? The determination of the study knee was assessed centrally from the original research log book.

The predicting (independent) variables

Knee MRI acquisition

High-resolution three-dimensional (3D) MRI acquisitions were obtained using 1.5 Tesla with integrated commercial knee coil. These examinations are optimised 3D spoiled gradient recalled acquisitions with fat suppression (General Electric, Milwaukee, Wisconsin, USA) or 3D fast imaging steady state precession acquisitions with water excitation (Siemens, Erlangen, Germany), as previously described.[12 18 28] Of note, for the fast imaging steady state precession sequence, the water excitation configuration was used instead of the fat suppression to optimise the acquisition time in which the repetition time/echo time are 22/9 ms instead of 42/7 ms, respectively.[29]

Associated predictors evaluation

The knee cartilage volume was measured as previously described.[12 18 19 30] The meniscal lesion (tear and extrusion) and BML evaluations were performed at baseline, as previously described.[31]

Knee x-ray (Lyon Schuss)

The joint space width (JSW) of the target knee was evaluated at baseline and 2 years in the medial tibiofemoral compartment using an automated computerised method, as previously described.[18 32]

Clinical evaluation

Patients were assessed at baseline and 2 years for height, weight and body mass index (BMI) as well as disease symptoms using the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) for pain, stiffness, function and total score,[33] visual analogue scale for patient global assessment (0 = very good; 100 = very bad) and the pain experienced on the day of the visit (patient pain score: 0 = no pain; 100 = most severe pain). There was a 24 h washout of analgesic medications before the clinical evaluation.

Serum biomarkers

Blood samples were collected and the levels of C-reactive protein (CRP), interleukin 6, matrix metalloproteinase (MMP) 1, MMP-3, type 1 collagen C-terminal telopeptide (CTX) I, CTX-II and cartilage oligomeric matrix protein were assessed for each serum sample collected at baseline and 2 years, as previously described.[15]

Statistical analysis

Data were entered into a computerised database using a blinded double-entry procedure, after which descriptive statistics for patient characteristics were tabulated. The primary efficacy outcome measure comparing structure modification of licofelone with naproxen was the rate of TKR of the studied joint in patients who had taken the study medication throughout the entire study period and who had had all the outcome (clinical and structural) evaluations collected, thus defined as the ATP cohort. The TKR incidence assessment was performed approximately 2–5 years (mean follow-up after study completion of 4.64 years±1.24) after study completion, which represents 4–7 years after patient enrolment and drug allocation. Univariate and multivariate logistic regressions were performed using the ATP cohort to find baseline predictors of TKR. The same analyses were performed to predict the overall TKR rate using the 2-year changes in variables. The magnitude of such an association was expressed in OR and their CI. Fisher's exact test was used for the rare instances in which the logistic regression did not yield any results. The Kaplan–Meier survival analysis was also used to compare the cumulative incidences of TKR over time between the two treatment groups. A log-rank test was used to compare the survival curves. Cox regression analysis was used to find predictors using survival of not having a TKR over time as an outcome. All statistical analyses were performed using SAS software, version 9.1. All tests were two-sided, and a p value of 0.05 or less was considered statistically significant. Analyses were not adjusted for multiple comparisons.

RESULTS

Patient baseline characteristics and TKR

From the ATP population of the original study,[18] 123 patients (76.3%) were contacted, of whom 18 (14.6%) had undergone TKR of the study knee. Eight patients (6.5%) had TKR of the contralateral knee but were not considered in the present analysis because no data were collected on the contralateral knee. Of note, no centre effect was seen in the incidence of TKR, reflecting a similar practice pattern among the six centres (p=0.637, univariate logistic regression, data not shown).

The effect of 2-year treatment with licofelone was moderately protective, as seven patients (39% of all tallied TKR) had the procedure compared with 11 patients (61%) treated with naproxen in the same time frame (p=0.232, univariate logistic regression). Patients from the two original treatment groups could be safely combined in the present post-hoc study, because they had similar baseline demographics and disease characteristics. Merging the two patient treatment groups provided the opportunity to achieve a meaningful sample size to explore a possible association between demographics, MRI and radiograph data and the occurrence of a TKR.

With regard to baseline demographics and symptom characteristics (table 1), patients who had a TKR (n=18) were mostly female, and had similar mean BMI and WOMAC scores compared with those who did not have the procedure (n=105). However, a trend towards greater TKR incidence was seen for older mean age (63.5 vs 59.8 years, p=0.076). The presence of higher CRP levels at baseline was a significant (p=0.049) predictor of TKR, whereas all the other biomarkers, cartilage oligomeric matrix protein, MMP-1, MMP-3, CTX-I, CTX-II and interleukin 6, were not (data not shown).

With regard to knee structural assessment, the baseline JSW (1.9 mm vs 3.5 mm, p=0.0008) was strongly associated with the occurrence of a TKR, whereas baseline cartilage volume, measured in the global knee, medial compartment or lateral compartment, was not associated with TKR. However, the presence of a severe medial tear (p=0.004) or medial extrusion (p=0.013) was highly correlated with subsequent TKR. These represent the highest OR: 5.687 (CI 1.750 to 18.490) and 4.058 (CI 1.346 to 12.233, univariate logistic regression) of TKR over time. Moreover, the presence of BML in the medial compartment (p=0.0003) or the medial plateau (p=0.0001) was very strongly associated with TKR.

Table 1 Baseline characteristics and predictors of target knee replacement—univariate analyses

	Knee replacement			If p value <0.05	
	Yes (n=18)	No (n=105)	p Value*	OR	(95% CI)
Male, % (no.)	44% (8)	34% (36)	0.408		
Age (years), mean (SD)	63.5 (6.1)	59.8 (8.4)	0.076		
BMI (kg/m^2), mean (SD)	31.9 (3.9)	32.1 (6.4)	0.919		
WOMAC, mean (SD)					
Baseline pain	52.8 (10.9)	57.6 (11.4)	0.105		
Stiffness	62.2 (19.3)	62.2 (17.9)	0.999		
Function	54.4 (17.1)	55.2 (16.0)	0.839		
Total	54.7 (14.3)	56.3 (13.7)	0.650		
CRP biomarker (mg/l), mean (SD)	13.7 (12.7)	7.3 (11.6)	0.049	1.035	(1.000 to 1.071)
Treatment effect, % (no)			0.232		
Licofelone	39% (7)	54% (57)			
Naproxen	61% (11)	46% (48)			
Joint space width, mean (SD)	1.9 (2.0)	3.5 (1.7)	0.0008	0.579	(0.420 to 0.797)
MRI cartilage volume (mm^3), mean (SD)					
Medial compartment	5292 (1499)	5736 (1672)	0.291		
Lateral compartment	6401 (1948)	6230 (1718)	0.701		
Global knee	11693 (3247)	11966 (3180)	0.736		
Meniscal lesion, % (no)					
Lateral tear	83% (15)	65% (68)	0.132		
Severe lateral tear	22% (4)	22% (23)	0.976		
Medial tear	100% (18)	83% (87)	0.072†		
Severe medial tear	78% (14)	38% (40)	0.004	5.687	(1.750 to 18.490)
Medial extrusion	72% (13)	39% (41)	0.013	4.058	(1.346 to 12.233)
BML score, mean (SD)					
Medial plateau	1.8 (1.3)	0.7 (1.0)	0.0003	2.201	(1.434 to 3.377)
Medial compartment	4.2 (3.2)	1.5 (2.0)	0.0001	1.484	(1.213 to 1.815)
Lateral compartment	0.6 (1.2)	0.4 (1.2)	0.623		
Femoropatellar compartment	0.8 (1.3)	1.2 (1.8)	0.379		
Global knee	5.6 (4.7)	3.1 (3.0)	0.010	1.196	(1.043 to 1.370)

*Logistic regression to predict a knee (target) replacement.
†Fisher's exact test.
BMI, body mass index; BML, bone marrow lesion; CRP, C-reactive protein; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

Univariate analysis of change in variables at 2 years and risk of TKR

The improvement of symptoms was less in patients who had the surgery (table 2). The mean improvement in the WOMAC pain score was −11.4 in TKR patients versus −28.8 for the others (p=0.009). Similarly, improvement in the WOMAC function (p=0.023) and total (p=0.026) scores was less in the TKR group. The changes in biomarker levels were not associated with the occurrence of a TKR (CRP, p=0.202) (data not shown for the other biomarkers). The reduction in the JSW at the 2-year follow-up was strongly associated with a TKR, as a loss of 7% or greater was seen in almost all TKR candidates (94% vs 52% for the non-candidates, p=0.009) with an OR of 15.454 (CI 1.984 to 120.388). The loss of cartilage volume in the medial compartment (≥8%, p=0.005) and global knee (≥8%, p=0.034) was also very strongly associated with TKR, whereas a volume loss of at least 8% in the medial compartment was associated with the highest OR (18.700, CI 2.401 to 145.669) for a TKR. None of the BML changes at the 2-year follow-up were associated with TKR.

Multivariate analyses of change in variables at 2 years and risk of TKR

The baseline variables used in the multivariate logistic model for predicting a TKR are presented in table 3. Severe medial meniscal tear (OR 4.624, p=0.023) and the presence of BML on the medial plateau (OR 1.808, p=0.025) were the most significant. Medial meniscal extrusion also showed a trend (OR 3.073, p=0.070). The reduction of at least 8% of the cartilage volume in the medial compartment was associated with an OR of 9.062 for a TKR (CI 0.943 to 87.085, p=0.056). These variables, therefore, were all significant while correcting for important confounding factors such as age, gender, BMI and WOMAC pain.

When including both baseline values and 2-year changes for all the variables (table 3), the baseline medial meniscal lesions (severe medial tear (OR 5.351, p=0.008) and extrusion (OR 3.894, p=0.021)) were the most strongly associated with TKR. To a lesser extent, the worsening of the WOMAC pain score at 2 years was also independently associated (OR 1.022, p=0.069) with knee surgery. Of note, there was no association of treatment (licofelone vs naproxen) with TKR according to these multivariate analyses.

Survival analyses: risk of TKR over time

The length of time after a patient was enrolled in the study and the influence of treatment (licofelone vs naproxen) on the occurrence of a TKR were examined. The Kaplan–Meier survival curves for patients are presented in figure 1. Over time (at approximately 4 years), the two curves tend to separate from each other favouring a protective effect of licofelone versus naproxen. Despite the small number of TKR that occurred (n=18), a log-rank test revealed a trend towards significance (p=0.150). A multivariate Cox regression model to assess the independence of the effect of this treatment (table 4) demonstrated that the protective effect of licofelone against the occurrence of a TKR was maintained, with an OR of 0.474, p=0.147. While correcting for age, gender and BMI, only age was associated with the occurrence of a TKR over time; OR 1.059, p=0.091.

Table 2 Variable 2-year change and risk of target knee replacement—univariate analyses

	Knee replacement			If p value <0.05	
	Yes (n=18)	No (n=105)	p Value*	OR	(95% CI)
WOMAC, mean (SD)					
Total	−11.6 (28.9)	−27.7 (23.6)	0.026	1.027	(1.003 to 1.051)
Pain	−11.4 (26.9)	−28.8 (24.3)	0.009	1.028	(1.007 to 1.049)
Stiffness	−17.4 (32.3)	−30.5 (26.5)	0.069		
Function	−9.7 (29.7)	−26.8 (24.5)	0.023	1.027	(1.004 to 1.050)
CRP biomarker (mg/l), mean (SD)	−28.9 (52.8)	−4.5 (76.6)	0.202		
JSW reduction ≥7%, % (no)	94% (17)	52% (55)	0.009	15.454	(1.984 to 120.388)
Cartilage volume, % (no)					
Medial compartment					
Reduction of at least 8%	94% (17)	48% (50)	0.005	18.700	(2.401 to 145.669)
Lateral compartment					
Reduction of at least 5%	56% (10)	51% (54)	0.746		
Global knee					
Reduction of at least 7%	78% (14)	50% (52)	0.034	3.567	(1.101 to 11.552)
BML score, mean (SD)					
Medial compartment	0.4 (2.2)	0.3 (1.2)	0.801		
Lateral compartment	0.1 (0.7)	0.2 (0.7)	0.449		
Femoropatellar compartment	0.0 (0.4)	0.3 (0.7)	0.109		
Global knee	0.5 (2.5)	0.8 (1.6)	0.493		

*Logistic regression to predict a knee (target) replacement.
BML, bone marrow lesion; CI, confidence interval; CRP, C-reactive protein; JSW, joint space width; OR, odds ratio; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

Table 3 Predictors of target knee replacement—multivariate analyses

	OR	95% CI	p Value*
Baseline predictors only			
Male	1.189	0.341 to 4.149	0.786
Age (years)	1.041	0.949 to 1.142	0.396
BMI (kg/m^2)	0.992	0.893 to 1.101	0.876
WOMAC pain	0.968	0.916 to 1.023	0.255
Severe medial meniscal tear	4.624	1.236 to 17.297	0.023
Medial meniscal extrusion	3.073	0.914 to 10.332	0.070
BML medial plateau	1.808	1.077 to 3.034	0.025
JSW minimum (mm)	0.752	0.518 to 1.093	0.136
Variables, baseline value and 2-year change			
Male	1.679	0.533 to 5.285	0.376
Age (years)	1.066	0.982 to 1.158	0.128
BMI (kg/m^2), change at 2 years	1.042	0.788 to 1.377	0.773
WOMAC pain, change at 2 years	1.022	0.998 to 1.045	0.069
Severe medial meniscal tear, baseline	5.351	1.543 to 18.629	0.008
Medial meniscal extrusion, baseline	3.894	1.230 to 12.326	0.021
Medial compartment cartilage volume reduction of ≥8% at 2 years	9.062	0.943 to 87.085	0.056
JSW reduction of ≥7% at 2 years	8.164	0.893 to 74.620	0.063

*Logistic regression to predict a knee (target) replacement.
BMI, body mass index; BML, bone marrow lesion; CI, confidence interval; JSW, joint space width; OR, odds ratio; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

DISCUSSION

The main aim of this post-hoc study was to examine the long-term effect of licofelone compared with naproxen on the occurrence of TKR in knee osteoarthritis patients. Similar studies have already been performed using TKR as an outcome and its feasibility has been demonstrated. Bruyère *et al*[27] demonstrated that in knee osteoarthritis patients, treatment with glucosamine sulfate for at least 12 months and up to 3 years may prevent the occurrence of a TKR in an average of 5 years after drug discontinuation. Moreover, Cicuttini *et al*[34] and Bruyère *et al*[35] demonstrated that the tibial osteoarthritis cartilage volume loss[34] and the JSN[35] were independently associated with subsequent TKR at 4 and 8 years of follow-up, respectively. Those studies are most relevant in the context of the current study as their design was very similar to ours. However, the present study also provides novel information on the protective effects of licofelone on the progression of knee osteoarthritis structural changes using the 'hard' outcome of TKR. Although the protective effect was statistically modest, a trend favouring licofelone was seen in both the endpoint incidence and survival analyses after approximately 4 years following study enrolment (or approximately 2 years after study completion). Approximately two-thirds of the TKR were performed in the naproxen group, the group that previously showed more rapid progression of the loss of cartilage volume.[18] The enrolment of a larger number of patients might have yielded even more convincing evidence. The current findings also indicate that patients who had TKR had greater incidences at baseline of severe meniscal extrusion, narrower JSW, more severe loss of cartilage volume and that these patients were treated mainly with naproxen. The fact that licofelone has been shown to abrogate in vivo the synthesis

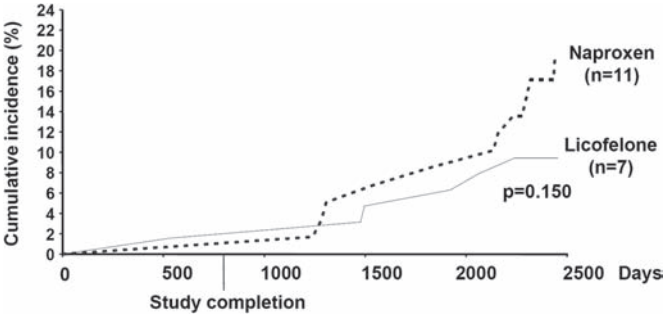

Figure 1 Kaplan–Meier cumulative incidence: replacement of target knee not adjusted for covariates. Cumulative incidence of having a total knee replacement on the study knee over time since the beginning of study enrolment per treatment group. Survival analysis was done using the Kaplan–Meier cumulative incidence method. The log-rank method was performed to assess statistical relevance between the two treatment groups.

of many osteoarthritis cartilage catabolic factors and inflammatory cytokines[36 37] may explain the differences in TKR incidence between the two treatment groups.

This study also validates the use of MRI in a multicentre study demonstrating its assessment of the effects of drug treatment translating into a 'hard' outcome such as a TKR. Data from MRI have also broadened our understanding of the role of meniscal alterations and BML as risk factors for rapid disease progression potentially impacting patient response to DMOAD treatment. Indeed, the difference between drug treatments in the occurrence of TKR might also have been dampened by these confounding factors that mandate patient stratification strategies. The relatively small number of patients in this analysis prevented such stratification. The findings of the present MRI study also raise the issue of the importance of considering patient inclusion based on risk factors for disease progression in the planning of a DMOAD trial. The present results and those from previous knee MRI studies[25 26] bring to light the importance of evaluating cartilage loss at earlier stages of the knee osteoarthritis process in the prediction of TKR. The medial compartment lesions at baseline such as the presence of meniscal lesions or BML were strongly predictive of TKR while a greater JSW was protective; data thus support the role played by biomechanical stress in such an event.

With the exception of age, the baseline demographics and clinical characteristics of the patients, contrary to the structural variables, did not predict the long-term occurrence of a TKR. The patient dropout rate from the original study at 2 years (over 40%), which was similar to other long-term osteoarthritis clinical trials,[4 6 38] might explain the lack of predictive power of these variables. The baseline levels of CRP, a marker of cartilage volume loss in this study,[15] were twice as high for those who subsequently had a TKR versus the controls. The cartilage volume loss, especially in the medial compartment, but not the baseline volume, was found to be strongly predictive of a TKR. These findings are in accordance with outcomes such as JSW, a medial compartment measurement, which have been demonstrated to be predictive of knee osteoarthritis progression.[35 39] Our previous study[18] revealed that the loss of cartilage volume was significantly less in patients treated with licofelone compared with naproxen. In the present analysis, a strong signal of lesser change in symptoms, particularly WOMAC pain, observed in the 2-year study is clearly seen in the TKR group. Recent publications have demonstrated that cartilage degradation in knee osteoarthritis patients is associated with worsening pain. A cartilage volume loss of a magnitude of 8–10% at 2 years was found to correlate with the worsening of the WOMAC pain variable.[31 40] The present study suggests that it may also predict the incidence of a TKR, a logical endpoint of such occurrence. However, information about what would be a clinically significant difference in cartilage loss prevention between two therapeutic interventions to prevent TKR remains to be revealed. Contrary to a previous report,[41] but in line with the recent meta-analysis of Yusuf *et al*,[42] BML change over time in our study was not associated with pain change or with the occurrence of subsequent TKR. Data from our previous studies[31 43] showed that BML were easily detected by the same MRI sequences used in this study, which were found to be at least as good as those used in other studies[44] at establishing correlations between BML, disease signs and symptoms, and the evolution of structural (cartilage) lesions in knee osteoarthritis patients.

This study has limitations. As this is a post-hoc analysis, a randomised controlled trial with TKR as the primary outcome would be mandatory to evaluate the protective effects of DMOAD agents. Another limitation related to the design of the original study is the absence of a placebo arm. For such a lengthy study, it would obviously have been unethical to treat patients with a placebo. The TKR indication and occurrence is obviously highly dependent on local medical and surgical practices, the availability of the procedure and patient preference. A surrogate variable such as 'indication of TKR' instead of the actual procedure was recently proposed[22] but is still susceptible to extreme variability and subjective appreciation. The phone interview probing the TKR occurrence did not assess the ultimate reason for the TKR, assuming that such a procedure is unique and such a basic question is well understood by patients. No specific attempt was made to retrieve medical charts to confirm that a TKR procedure was done. As the patients had completed the study and were no longer taking the experimental medication for at least 2 years, many additional reasons might have come into play to favour or prevent the occurrence of a TKR. The treatment allocation code was revealed to the investigators approximately 1 year after the last patient completed the 2-year phase of the trial. Such information was not systematically communicated to patients. However, as licofelone is not available in Canada, it is more than likely that such information was not confounding with regard to the occurrence of the TKR. However, the interviewers were blinded to the treatment allocation and results of the original study,[18] which probably precluded any biases that could have impacted the results. We did not attempt to retrieve additional information about the medications (non-steroidal anti-inflammatory drugs, analgesics, opioids, intra-articular injections) received, or superimposed traumatism or surgery once the patient completed the randomised controlled phase of the trial, which can impact the occurrence and timing of a TKR.

The cut-off values of JSW loss of 7% and medial cartilage volume change at 8% were selected a posteriori to yield the best prediction of TKR occurrence and were not predetermined before the analysis. Other trials used internal validity data of measurement tools such as the JSW. For instance, a trial using a bisphosphonate (risedronate) to prevent knee osteoarthritis progression[45] used the absolute value JSW loss of 0.6 mm from baseline (three times the SD of JSW measurement) as a definition of a 'progressor'. Similarly, others used a similar threshold of greater than 0.5 mm JSW loss over time to define progression.[5 6] This is clearly different from a percentage change that will yield different absolute change from one patient to another according to the JSW value at baseline. Our study was not intended to yield absolute cut-off as a predictor of TKR for future studies, but merely to understand the variables that should be considered when predicting such surgery.

Table 4 Predictors of time to target knee replacement—Cox regression

	Univariate			Multivariate		
	HR	95% CI	p Value*	HR	95% CI	p Value*
Licofelone	0.489	0.181 to 1.322	0.158	0.474	0.173 to 1.300	0.147
Male				1.576	0.599 to 4.143	0.357
Age (years)				1.059	0.991 to 1.132	0.091
Baseline BMI (kg/m^2)				1.018	0.942 to 1.099	0.655

*Cox regression to predict a knee (target) replacement.
BMI, body mass index; CI, confidence interval; HR, hazard ratio.

Finally, the paucity of TKR occurrences and the relatively small patient number (n=123) present additional study limitations. For instance, problems with multivariate analysis feasibility and interpretation may arise as we could not enter all variables in order for the model to hold statistically. Choices of variable had to be made, especially those that yield the best univariate associations and forcing in the model other important classic variables such as age, sex and BMI. The multivariate analyses explored the occurrence or not of a TKR at the time of the interview as a dependent variable. The Cox regression uses the time to TKR from study entry as a dependent variable. Both analyses probe very similar outcomes but caution is advised while trying to translate our results for future studies.

In summary, this study provides new information regarding the factors that could possibly predict the occurrence of TKR. These data demonstrate that, in a knee osteoarthritis clinical trial, it is possible to predict a 'hard' outcome such as TKR using clinical and MRI data. The results are highly encouraging and support the use of MRI to establish new outcomes in DMOAD trials.

Contributors The authors have read and approved the manuscript and contributed to the study design, data analysis, interpretation of data and drafting and revision of the manuscript. A data review committee (JPR, JPP, JMP) analysed the data and MD and JPR were responsible for the accuracy of the data.

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Competing interests JPR is a consultant for ArthroVision Inc., MD is a consultant for ArthroLab Inc., JMP and JPP are consultants for and shareholders in ArthroLab Inc. and ArthroVision Inc. BH and DC received honoraria from ArthroLab Inc. FA is an employee of ArthroVision Inc.

Patient consent Obtained.

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