Severity of Joint Pain and Kellgren-Lawrence Grade at Baseline Are Better Predictors of Joint Space Narrowing Than Bone Scintigraphy in Obese Women with Knee Osteoarthritis

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ABSTRACT. ***Objective.*** To compare the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of a baseline late-phase bone scan and assessments of the radiographic and symptomatic severity of knee osteoarthritis (OA) at baseline as predictors of loss of articular cartilage thickness, as reflected in joint space narrowing (JSN) in the medial tibiofemoral compartment.

Methods. Subjects (174 obese women, 45–64 yrs of age, with unilateral knee OA) were a subset of a larger cohort who participated in a placebo controlled trial of a disease modifying OA drug. Uptake of technetium medronate (^{99m}Tc-MDP) in anteroposterior (AP) and lateral views of a late-phase bone scan was measured at baseline in a region of interest drawn around the medial tibia, and was adjusted for (i.e., expressed as a ratio to) uptake in a reference segment of the tibial shaft, which served as an internal standard. Each subject underwent a fluoroscopically standardized radiographic examination of the knees (semiflexed AP view) and a pain assessment with the WOMAC OA Index at baseline, 16 months, and 30 months.

Results. Controlling for baseline joint space width and treatment group, multiple linear regression models showed that the adjusted ^{99m}Tc-MDP uptake at baseline was a significant predictor of joint space narrowing (JSN) in the index knee at 16 months (b = 0.180, p = 0.015) and 30 months (b = 0.221, p = 0.049). In the contralateral knee, uptake was only a marginally significant predictor of JSN at 30 months (b = 0.246, p = 0.083). Uptake in the upper and middle tertiles of the distribution predicted subjects who would exhibit JSN ≥ 0.50 mm within 16 months with 65% sensitivity (PPV 23%) and 36% specificity (NPV 77%). In contrast, a prediction rule based solely on the presence of Kellgren-Lawrence grade 3 OA severity and greater than median WOMAC Pain score identified progressors with 65% sensitivity (PPV 48%) and 79% specificity (NPV 88%).

Conclusion. Although the level of adjusted ^{99m}Tc-MDP uptake was significantly associated with JSN in knees with established radiographic OA, baseline bone scintigraphy is inferior to the radiographic severity of OA and knee pain (alone or in combination) as a predictor of loss of articular cartilage in subjects with knee OA. (J Rheumatol 2005;32:1540–6)

Key Indexing Terms:
OSTEOARTHRITIS KNEE BONE SCINTIGRAPHY
PROGRESSION RISK FACTORS

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Supported in part by National Institutes of Health grants R01 AR43348, R01 AR43370, and P60 AR20582; and a grant from Procter & Gamble Pharmaceuticals.

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Accepted for publication March 29, 2005.

Considerable interest and effort is currently being directed to the identification of biomarkers of radiographic joint space narrowing (JSN) — the surrogate for loss of articular cartilage in osteoarthritis (OA). OA biomarkers will be particularly valuable if they permit accurate prediction of which patient with OA will exhibit significant progression of JSN in the near future and which will not. A validated biomarker of OA will have immediate utility as an eligibility criterion in clinical trials of purported disease modifying OA drugs (DMOAD). The more homogeneous the trial sample with respect to the likelihood of progression of JSN, the less costly the trial will be with respect to sample size and duration of treatment[1,2].

We have shown[3] that quantitative estimates of uptake and retention of a bone-seeking radiopharmaceutical [technetium medronate (^{99m}Tc-MDP)] in a late-phase bone scan of the medial tibia predicts JSN in the index knee of patients with unilateral radiographic changes of OA in the standing anteroposterior (AP) view. This finding is consistent with the results reported by Dieppe, *et al*[4], who noted that OA knees in which the scan did not show focal areas of retention of the radiopharmaceutical did not exhibit progression of OA over the ensuing 5 years. In comparison, in OA knees with focal areas of retention, the likelihood of disease progression within 5 years was approximately 50%[4]. However, unlike the results of Dieppe, *et al*[4], in which baseline radiographic variables did not predict JSN, our previous research indicated that radiopharmaceutical uptake was confounded by the radiographic severity of OA at baseline, and that progression of JSN could be predicted as accurately (and with less radiation exposure and cost) by the Kellgren-Lawrence (K-L) grade[5] as by bone scintigraphy.

This study extends our observations regarding radiographic and scintigraphic predictors of JSN in knee OA. It differs from our previous study in several important respects: Whereas the data we reported previously[3] were based upon an analysis of 86 subjects with knee OA, the present study includes an additional 88 subjects. Further, in addition to assessing scintigraphic uptake as a predictor of JSN, we have now assessed the severity of knee pain at baseline and have compared the utility of these biomarkers in knees with established radiographic evidence of OA to that in knees in which radiographic evidence of OA was absent at baseline. Finally, we replaced the automated measurements of joint space width (JSW) used in the previous study with manual measurements, which we have shown recently are much less susceptible to errors in magnification-correction than those resulting from digital image analysis[6].

MATERIALS AND METHODS

The procedures, radiation exposure, other research risks, and associated safeguards for this study were approved by the radiation safety committees and the institutional review boards affiliated with the 6 participating clinical research centers.

Subjects. Subjects in this study were 174 obese women, 45–64 years of age, with unilateral knee OA who were enrolled in a randomized placebo controlled trial (RCT) of a purported DMOAD (doxycycline) conducted at 6 clinical research centers in the United States[7]. All subjects were in the upper tertile of age-, race-, and sex-appropriate norms for body mass index (BMI) from the Second National Health and Nutrition Examination Survey[8]. Radiographic eligibility criteria required K-L grade 2 or 3 severity of knee OA[5] in the index knee and grade 0 or 1 in the contralateral knee in the standing AP view. The intrarater reproducibility of K-L grades, based on repeat readings of a random sample of 30 OA knees, was very high (κ = 0.87). To establish norms for the bone scan results, 10 healthy normal adult subjects (nonobese men and women with neither clinical nor radiographic knee OA) underwent bone scintigraphy.

Bone scintigraphy. This was an ancillary clinical study, in which participation was open to subjects in the doxycycline RCT on a first-come, first-served basis — regardless of treatment group. Volunteers underwent bone scintigraphy 3 h after injection of 20 mCi ^{99m}Tc-MDP (Bristol-Myers Squibb, Princeton, NJ, USA). Radiopharmaceutical uptake (counts/pixel) in AP and lateral images was measured in 5 regions of interest (ROI): the lateral femur, lateral tibia, medial femur, medial tibia, and patellofemoral (PF) joint. The ROI for the lateral femur in the AP image included the patella[3].

Uptake in each ROI was adjusted for (i.e., expressed as a ratio to) uptake in a standard-size reference segment drawn roughly at the junction of the proximal and middle thirds of the tibia, which served as an internal standard. The ROI in the tibial shaft was bounded medially and laterally by cortical bone and was distal to the region of cancellous subchondral bone in which turnover is increased in OA[9]. The interrater reproducibility (intraclass correlation) of adjusted estimates of ^{99m}Tc-MDP uptake was determined previously to be 0.93[3]. Based on our previous study, where the medial tibia was the only ROI in which uptake of ^{99m}Tc-MDP predicted JSN in OA knees[3], uptake in the medial tibia was the focus of the present study.

Knee radiography. Each subject underwent a fluoroscopically standardized radiographic examination at baseline, according to the procedures and quality-control criteria for the fluoroscopically assisted semiflexed AP view[10,11]. Followup knee radiographs were obtained 16 months and 30 months after baseline.

Minimum JSW in the medial tibiofemoral compartment was measured by one of the investigators (SAM) with a screw-adjusted calipers and magnifying lens with graticule by the method of Lequesne[12]. JSW measurements were corrected for radiographic magnification, based on the measured diameter of a 6.35 mm steel ball encased in methyl methacrylate that was affixed with tape to the skin over the head of the fibula and served as a magnification marker. The standard error of JSW measurements made on radiographs satisfying quality-control criteria of the semiflexed AP protocol, based on repeated examinations performed within 7–10 days of each other, has been established to be ± 0.25 mm[13], with a 95% confidence interval (CI) for individual estimates of JSW equal to ± 0.50 mm. The intra- and interreader reproducibility of repeated manual measurements of magnification-corrected JSW in a random sample of 30 radiographs on which all identifying information was masked was excellent (intraclass correlation coefficient = 0.99 and 0.96, respectively)[6].

Pain assessment. Knee pain at baseline was measured with the Pain subscale of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC; 5-point Likert version)[14]. Pain in index and contralateral knees was assessed separately after washout (5 half-lives) of all nonsteroidal anti-inflammatory drugs and analgesics taken by the subject for knee pain or other reasons.

Statistical analysis. Index and contralateral knees were compared with respect to baseline JSW and ^{99m}Tc-MDP uptake using paired t tests. Generalized estimating equations (GEE) were used to compare the scintigraphic data for knees of the control subjects with those for the index and contralateral knees of the subjects with OA. The association between bone scintigraphy and JSN was examined using multiple linear regression. The dependent variable, JSN, was the difference between estimates of minimum

medial compartment JSW measured at baseline and followup. Treatment group (active treatment vs placebo) was included as a dichotomous variable. Baseline JSW also was included in the regression equation. Index and contralateral knees were analyzed separately.

The utility of bone scintigraphy and other possible markers of OA progression (K-L grade, pain score) was expressed in terms of standard parameters for diagnostic tests: sensitivity is the proportion of true progressors identified by a dichotomous predictor; specificity is the proportion of true nonprogressors identified by a dichotomous predictor. Positive predictive value (PPV) is the proportion of predicted progressors who actually progressed, and negative predictive value (NPV) is the proportion of predicted nonprogressors who did not progress. These values were calculated only on subjects from the placebo group of the parent randomized clinical trial. Subjects were classified as progressors at 16 months and 30 months if the respective JSN estimates were ≥ 0.50 mm (i.e., a decrease in JSW beyond the limits of the 95% CI of the baseline value)[13]. Estimates of the diagnostic parameters of bone scintigraphy at specific cutoff points in the distribution (i.e., 33rd, 50th, 66th percentile) were compared to those derived from data for the overall radiographic severity of knee OA at baseline (i.e., K-L grade 3 vs grade 2) and the severity of knee pain at baseline (WOMAC Pain score > vs ≤ the median value of the sample). The threshold value for pain was based on inspection of a scatterplot of WOMAC pain scores against 30 month JSN values.

RESULTS

Demographic, clinical, and radiographic characteristics of the subjects in this study are shown in Table 1. Eighty-four percent of the entirely female sample was white. Mean age (± SD) was 55.6 ± 5.7 years and mean BMI (± SD) was 36.0 ± 5.9 m/kg^2. One hundred (57%) of the 174 subjects exhibited K-L grade 2 OA severity in the index knee; 64% had grade 0 OA severity in the contralateral knee. Minimum medial JSW was significantly smaller in the index knee than in the contralateral knee ($p < 0.0001$). Mean adjusted ^{99m}Tc-MDP uptake in the medial tibia of the index knee (1.7:1) and of the contralateral knee (1.4:1) were both significantly greater than that observed in 20 normal control knees (1.2:1; $p < 0.0001$ and $p < 0.05$, respectively). In addition, mean uptake in the index knee was significantly greater in index knees than contralateral knees ($p < 0.0001$; Table 1).

Table 1. Characteristics of subjects at baseline.

No. of subjects	174
Age, yrs, mean ± SD	55.6 ± 5.7
Race, % Caucasian	84
Body mass index, kg/m^2, mean ± SD	36.0 ± 5.9
WOMAC Pain score, range 5–25, mean ± SD	
Index knee	11.5 ± 4.4
Contralateral knee	9.3 ± 4.2
Overall severity of tibiofemoral OA, index knee*	
Kellgren-Lawrence grade II, %	57
Kellgren-Lawrence grade III, %	43
Overall severity of tibiofemoral OA, contralateral knee*	
Kellgren-Lawrence grade 0, %	64
Kellgren-Lawrence grade I, %	36
Minimum medial joint space width, mm, mean ± SD†	
Index knee	3.6 ± 1.2
Contralateral knee	4.0 ± 0.9
Adjusted ^{99m} Tc-MDP uptake, mean ± SD††	
Medial tibia, index knee	1.7 ± 0.6
Medial tibia, contralateral knee	1.4 ± 0.4

* Graded in the standing AP view. † Measured in the semiflexed AP view. †† Adjusted for uptake in the mid-shaft of the tibia.

Followup semiflexed AP radiographs were obtained on 154 subjects (89%) at 16 months and 148 (85%) at 30 months. In the index knee, mean JSN (± SD) was 0.17 ± 0.46 mm over 16 months (0.13 mm/yr) and 0.35 ± 0.68 mm over 30 months (0.14 mm/yr). In comparison, mean JSN in the contralateral knee was 0.26 ± 0.50 mm over 16 months (0.20 mm/yr) and 0.41 ± 0.64 mm over 30 months (0.16 mm/yr). The more rapid rate of JSN in the contralateral knee reflects the effect of the active treatment in slowing JSN in the index knee, but not the contralateral knee[15].

Prediction of variability in JSN. The results of multiple regression analyses of JSN in the index knee are presented in Table 2. After controlling for baseline JSW and treatment group, the adjusted ^{99m}Tc-MDP uptake in the medial tibia was a significant predictor of medial JSN at 16 months ($p = 0.015$). The parameter estimate (b), or slope of the regression line, for adjusted uptake (0.18 mm/unit of uptake) indicates only a weak association between the variables. Multiple R^2 for the full regression equation was 0.090; inclusion of adjusted uptake in the equation increased R^2 by only 0.037. The association remained statistically significant at 30 months ($b = 0.221$ mm/unit, $p = 0.049$).

^{99m}Tc-MDP uptake in the contralateral knee at baseline was unrelated to medial JSN at 16 months (Table 2), although a marginally significant association between baseline uptake and JSW was observed after 30 months ($b = 0.246$ mm/unit of uptake, $p = 0.083$).

Dichotomous prediction of progression of JSN. All computations of sensitivity, specificity, PPV, and NPV are based on the following observations among the subset of subjects in the present study who were randomized to the placebo group of the DMOAD trial: 17 of 73 subjects exhibited JSN > 0.50 mm (i.e., beyond the 95% CI of the baseline estimate of JSW) in the index knee at 16 months; 23 of 70 subjects did so at 30 months.

Table 3 shows the results of dichotomous predictions of progression or lack of progression of JSN in the index knee at 16 and 30 months, based on percentile values for adjusted ^{99m}Tc-MDP uptake at baseline among all subjects in the study. Forty-seven subjects from the placebo group of the parent trial had uptake in excess of the 33rd percentile (1.39:1). These included 11 true-positives (sensitivity = 11/17, 65%) and 36 false-positives (PPV = 11/47, 23%). The lower tertile of medial tibial uptake comprised 26 subjects, including 20 of 56 nonprogressors (specificity = 36%) and 6 false-negatives. The NPV was 77% (20/26). By 30 months, sensitivity, PPV, and specificity of predictions based on uptake > 33rd percentile had improved slightly, while NPV remained essentially unchanged (Table 3).

More selective prediction criteria for bone scan results (i.e., uptake > 50th and > 66th percentiles) progressively

Table 2. Parameter estimates *(b)* and 95% confidence intervals (CI) from multiple linear regression analyses to predict variation in JSN.

	Independent Variable	16 Month JSN		30 Month JSN	
		b, mm/unit	95% CI	*b*, mm/unit	95% CI
Index knee	Baseline JSW, mm	0.012	–0.058 to 0.081	–0.015	–0.121 to 0.092
	Treatment group*	–0.191	–0.331 to –0.051	–0.279	–0.493 to –0.066
	Adjusted^{99m} Tc-MDP uptake†	0.180	0.036 to 0.323	0.221	0.003 to 0.439
Contralateral knee	Baseline JSW, mm	0.075	–0.010 to 0.160	0.083	–0.033 to 0.198
	Treatment group*	–0.032	–0.190 to 0.126	0.077	–0.128 to 0.283
	Adjusted^{99m} Tc-MDP uptake†	0.146	–0.073 to 0.364	0.246	–0.030 to 0.521

* 1 = Active treatment, 0 = placebo. † Ratio of uptake in a region of interest (ROI) drawn around the medial tibia to that in a ROI in the midshaft of the tibia (internal standard). JSN: joint space narrowing, JSW: joint space width.

decreased the sensitivity of predictions, but increased specificity at both followup examinations (Table 3). However, the more selective bone scan criteria did not markedly improve the PPV of bone scan results. In predictions based on each percentile value, true-positives represented only about 25% of those predicted to exhibit JSN ≥ 0.50 mm at 16 months.

Table 3 also includes analyses of predictions based on the severity of radiographic knee OA and knee pain at baseline. Among the 73 subjects in the placebo group who underwent a radiographic examination at 16 months, 36 had K-L grade 3 OA at baseline. These included 12 true-positives (sensitivity = 71%). True-positives represented a larger proportion of those predicted to exhibit progression of JSN at 16 months (PPV = 33%) than in any of the scintigraphy-based predictions. Specificity and NPV of predictions based on K-L grade 3 (57% and 86%, respectively) were comparable to, or greater than, those obtained with bone scans.

Comparable results were found in 16 month predictions based on a WOMAC Pain score higher than the median value for the sample (i.e., > 11 on a scale of 5–25, Table 3). Unlike the sensitivity of predictions based on bone scintigraphy, that of predictions based on the K-L grade or WOMAC pain score did not increase between 16 and 30 months. However, PPV of the K-L grade or WOMAC score increased with time, such that by 30 months, predictions were identifying true-positive and false-positive progressors in roughly equal proportion.

Because information on the radiographic severity of OA and knee pain are generally available during screening for OA clinical trials, a determination of eligibility based on both criteria comes at no additional cost, compared to a determination based on only one of these 2 variables. Therefore, it is noteworthy that 23 subjects had K-L grade 3 OA and a WOMAC pain score > 11 at baseline. Eleven showed JSN ≥ 0.50 mm at 16 months (sensitivity = 65%). More important, the combination of K-L grade 3 and WOMAC Pain score > 11 resulted in only 12 false-positives at 16 months (PPV = 48%). By 30 months, the PPV had increased to 60%.

To examine the marginal additional utility of bone scintigraphy as a predictor of the progression of JSN beyond that possible with baseline data on radiographic severity of OA and knee pain, we estimated the diagnostic test parameters of 2 alternative prediction rules, as follows.

By the first rule, likely progressors were those with K-L grade 3 OA, a WOMAC Pain score > 11, and adjusted ^{99m}Tc-MDP uptake in the upper or middle tertile of the distribution (i.e., > 33rd percentile). As shown in Table 3, the sensitivity, specificity, and predictive value of this rule is essentially equivalent to that for predictions based on the combination of K-L grade and WOMAC score.

By the second rule, likely progressors were those with K-L grade 3 OA and WOMAC Pain score > 11 or adjusted ^{99m}Tc-MDP uptake in the upper tertile of the distribution (i.e., > 66th percentile), regardless of K-L grade and WOMAC score. This set of criteria identified 11 of 17 progressors at 16 months (worse than with K-L grade or WOMAC score alone). The addition of data from bone scintigraphy resulted in decreases in PPV, specificity, and NPV, relative to that achieved by using radiographic severity and knee pain without scintigraphy. The tradeoff between identification of true-positive to false-positive progressors by these rules at 16 months did not improve notably at 30 months (Table 3).

DISCUSSION

Our choice of specific threshold values for analyzing the predictive utility of bone scintigraphy was governed, in part, by precedent and, in part, by the desire to inform practical decision-making in clinical trials. We selected the 33rd percentile as a threshold value for radiopharmaceutical uptake because the "cold scan" identified by Dieppe, *et al*[4] as having perfect NPV (i.e., no false-negative progressors) occurred in about one-third of the OA patients studied. To determine whether the tradeoff of sensitivity and specificity varied across a clinically important range of possible threshold values, we also evaluated the prognostic accuracy of uptake above the 50th and 66th percentiles. Our decision not to examine threshold values less than the 33rd and greater than the 66th percentile was based on practical considerations: for the purpose of identifying likely progressors for, e.g., a DMOAD trial, the utility of a costly and invasive

Table 3. Sensitivity, positive predictive value (PPV), specificity, and negative predictive value (NPV) of bone scintigraphy, radiography, and knee pain as predictors of JSN ≥ 0.50 mm in the index knee.

Predictor	Diagnostic Parameters* (%) Month 16, n = 73	Month 30, n = 70
Adjusted medial tibial uptake > 33rd percentile		
Sensitivity	11/17 (65)	17/23 (74)
PPV	11/47 (23)	17/45 (38)
Specificity	20/56 (36)	17/47 (40)
NPV	20/26 (77)	19/25 (76)
Adjusted medial tibial uptake > 50th percentile		
Sensitivity	8/17 (47)	13/23 (57)
PPV	8/34 (24)	13/32 (41)
Specificity	30/56 (54)	28/47 (60)
NPV	30/39 (77)	28/38 (74)
Adjusted medial tibial uptake > 66th percentile		
Sensitivity	7/17 (41)	11/23 (48)
PPV	7/28 (25)	11/25 (44)
Specificity	35/56 (63)	33/47 (70)
NPV	35/45 (78)	33/45 (73)
Baseline K-L grade 3 OA		
Sensitivity	12/17 (71)	15/23 (65)
PPV	12/36 (33)	15/32 (47)
Specificity	32/56 (57)	30/47 (64)
NPV	32/37 (86)	30/38 (79)
Baseline WOMAC pain > 11		
Sensitivity	13/17 (77)	15/23 (65)
PPV	13/36 (36)	15/33 (45)
Specificity	33/56 (59)	29/47 (62)
NPV	33/37 (89)	29/37 (78)
K-L grade 3 OA and WOMAC pain > 11		
Sensitivity	11/17 (65)	12/23 (52)
PPV	11/23 (48)	12/20 (60)
Specificity	44/56 (79)	39/47 (83)
NPV	44/50 (88)	39/50 (78)
K-L 3 and WOMAC > 11 and uptake > 33rd percentile		
Sensitivity	10/17 (59)	11/23 (48)
PPV	10/21 (48)	11/19 (58)
Specificity	45/56 (80)	39/47 (83)
NPV	45/52 (87)	39/51 (76)
(K-L 3 and WOMAC > 11) or uptake > 66th percentile		
Sensitivity	11/17 (65)	15/23 (65)
PPV	11/35 (31)	15/31 (48)
Specificity	32/56 (57)	31/47 (66)
NPV	32/38 (84)	31/39 (79)

* Sensitivity = n of true-positive progressors/total n of true progressors; PPV = n of true-positive progressors/false-positive progressors; specificity = n of true-negative progressors/total n of true nonprogressors; NPV = n of true-negative progressors/total n of true-negative and false-negative progressors.

prognostic procedure would be diminished markedly if it excluded very few (or included virtually all) otherwise qualified subjects.

By the same token, we chose not to examine all possible pairwise comparisons of data from bone scan, radiography, and pain assessments in favor of the combinations that are most commonly available in the course of enrollment of subjects for a clinical trial in knee OA. Generally, eligibility for such trials is determined on the basis of radiographic and clinical diagnostic criteria. The practical question is whether diagnostic accuracy based on these relatively benign and inexpensive assessments can be improved by addition of the more invasive and costly bone scan. Even if we had found, for example, that the combination of bone scintigraphy and pain assessment provided the optimal balance of sensitivity and specificity with respect to progression of JSN, it is unlikely that the clinical OA research community would accept a recommendation to disregard radiographic evidence of knee OA when determining subject eligibility.

Retention of a bone-seeking radiopharmaceutical in a

late-phase bone scan of osteoarthritic joints has been extensively documented[16-21]. Although an abnormal bone scan may reflect osteophytosis[18], it can also signal turnover of subchondral bone, which may be of pathogenetic significance in OA[22]. Abnormal patterns of retention of a radiopharmaceutical have been shown to correlate with "bone marrow edema" in T2-weighted fat-saturated magnetic resonance (MR) images[23]. This MRI abnormality — particularly when seen in the medial tibia — has been associated cross-sectionally with knee pain[24] and longitudinally with progression of JSN[25].

The potential of bone scintigraphy as a biomarker of progression of OA (i.e., as a means by which to exclude from a DMOAD study subjects who are unlikely to exhibit structural progression of OA in the near future) has received considerable attention. Dieppe, *et al*[4] demonstrated that knee OA did not progress structurally over a 5 year period in subjects with knee OA whose late-phase bone scan failed to show an abnormal pattern of retention (i.e., high NPV of the bone scan). In contrast, among subjects whose bone scan showed retention of the radiopharmaceutical, approximately half exhibited progression of knee OA (i.e., PPV $\approx$ 50%)[4].

In our study, ^{99m}Tc-MDP uptake was not graded dichotomously, but was quantified and the results were expressed as a continuous variable, with the counts per pixel in the medial tibial plateau related to those in an area of the tibia remote from the joint.

Our patient group differed considerably from that studied by Dieppe, *et al*[4] insofar as our cohort was exclusively female, markedly obese (mean BMI = 36.0 ± 5.9), and had evidence of OA in only one knee at baseline, based on the conventional standing AP radiograph. In contrast, the cohort analyzed by Dieppe, *et al*[4] was 31% male, only 27% had a BMI = 30, and 55% had bilateral radiographic knee OA at baseline. The generalizability of the scintigraphy results in our study, therefore, needs to be determined.

A limitation of the study by Dieppe, *et al*[4] was that the absence of reproducible positioning standards for the conventional extended view knee radiograph used in that study necessitated an extremely conservative definition of disease progression (i.e., JSN $\geq$ 2 mm or knee arthroplasty within 5 yrs). It is unknown whether results of a bone scan can distinguish progressors from nonprogressors within shorter intervals (i.e., 2–3 yrs) that represent the practical limit of the duration of a DMOAD trial[2].

In our previous study, after controlling for age, BMI, and the K-L grade of radiographic severity, the level of ^{99m}Tc-MDP uptake in the index knee of subjects in the placebo group was not significantly associated with the rate of JSN at 16 months[3]. In contrast, the results of the present study, based on analysis of both treatment groups and more precise, manual measurements of JSN, indicate that adjusted ^{99m}Tc-MDP uptake in the medial tibia of the index knee at baseline was significantly associated with medial compartment JSN at both 16 months and 30 months. However, as indicated by the slopes of the regression lines for the 16 month and 30 month analyses (i.e., 0.180 and 0.221 mm/unit of adjusted uptake, respectively) and the SD of uptake in the index knee at baseline (0.6 units), at both time intervals the association was weak.

Our previous study did not include an analysis of the contralateral knee, in which definite radiographic evidence of knee OA in the standing AP radiograph was not present at baseline. The present study shows that the association between ^{99m}Tc-MDP uptake and JSN in the contralateral knee was, like that in the index knee, weak (b = 0.146 mm/unit of uptake at 16 mo and 0.246 mm/unit at 30 mo) and only marginally significant at the end of the study.

The mean rate of JSN in the contralateral knee in the present study (0.16–0.20 mm/yr) was comparable to that in the index knee. Our observation that the adjusted uptake of ^{99m}Tc-MDP at baseline in the contralateral knee is greater than that in controls confirms it is not a normal joint. However, results of the baseline bone scan were even less predictive of JSN in the contralateral knee than in the index knee.

These data indicate that a baseline bone scan is of little practical utility as a biomarker of loss of articular cartilage in subjects with knee OA. Across a wide range of the distribution of subjects with respect to adjusted ^{99m}Tc-MDP uptake (i.e., from the 33rd to the 66th percentile) the prediction of likely progressors at 16 months yielded true-positives and false-positives in a consistent ratio of 1:3. In contrast, predictions based on a conventional radiographic assessment (K-L grade 3) or on a standardized pain assessment (WOMAC pain score > 50th percentile) identified true-positive and false-positive progressors at 16 months in a ratio of 1:2. That the severity of joint pain is a risk factor for the progression of radiographic changes of OA was noted by Spector, *et al*[26] and more recently by Wolfe and Lane[27]. As in these studies, the analysis of baseline knee pain alone as a predictor of JSN in our study is limited because all subjects in this trial had radiographic knee OA at baseline. Therefore, the accuracy of predictions based solely on the baseline WOMAC Pain score are generalizable only to subjects who are known *a priori* to have K-L grade 2 or grade 3 severity of knee OA.

It should also be noted that subjects in the doxycycline RCT were recruited from the community and had lower pain scores, on average, than are seen in samples drawn from the clinic[7,15]. We would not presume that the threshold value for this sample (i.e., the median) would be the optimal point within the distribution of baseline pain scores to separate progressors from nonprogressors in more symptomatic clinical OA populations.

The PPV was improved notably by combining information on radiographic severity and pain; in predictions based on the presence of K-L grade 3 and a level of knee pain

greater than the median value at baseline, true-positive and false-positive progressors at 16 months were identified in roughly equal proportion. The accuracy of these predictions was not improved further by addition of information from the bone scan.

In conclusion, adjusted ^{99m}Tc-MDP uptake in the medial tibia was significantly associated with medial compartment JSN in the index knee of our subjects. However, baseline bone scintigraphy was inferior to the combination of radiographic severity of OA and severity of knee pain in predicting loss of articular cartilage in subjects with knee OA.

ACKNOWLEDGMENT

We gratefully acknowledge the efforts of a dedicated group of study coordinators whose skills were essential in assuring the successful conduct of this multicenter study: Autumn Bill, Cherita Fagan, Nancy Flowers, Johnny Fuessler, Dot Gunter, Jenny Hixon, Julie Johnson, Sherrie Pryber, Linda Ragozzino, Andrea Schaffter, Edie Sparr, and Kathy Urbansky.

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