COMPARISON OF QUANTITATIVE AND SEMI-QUANTITATIVE INDICATORS OF JOINT SPACE NARROWING IN SUBJECTS WITH KNEE OSTEOARTHRITIS

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ABSTRACT

**Objective:** To compare quantitative estimates of change in joint space width (JSW) with semi-quantitative ratings of the progression of joint space narrowing (JSN) with respect to their sensitivity to change over time.

**Methods:** Subjects were 431 obese women 45–64 years old with unilateral radiographic knee OA who were randomized to 30 months of treatment with doxycycline 100 mg twice a day or placebo. Quantitative estimates of change in JSW in the medial tibiofemoral compartment were derived from manual measurements of joint space width in fluoroscopically assisted semiflexed anteroposterior (AP) radiographs obtained at baseline and 16 and 30 months after randomization. Radiographic JSN was rated (0-3 scale) in the same images by 2 readers using a standard atlas. Changes in overall severity of knee OA (Kellgren and Lawrence criteria) were derived from gradings of conventional standing AP radiographs obtained at baseline and 30 months. The above readings were performed with the readers blinded to treatment group and to the chronologic order of the exams. In addition, a gestalt judgment of the progression of JSN was made after the semiflexed AP radiographs were unblinded with respect to sequence.

**Results:** Follow-up radiographs were obtained from 381 subjects (88%) at 16 months and 367 subjects (85%) at 30 months. Mean loss of JSW was significantly lower in subjects treated with doxycycline than in the placebo group (0.15 vs. 0.30 mm at 16 months; 0.24 vs. 0.45 mm at 30 months; \( P < 0.05 \) at both times). However, the treatment groups did not differ with respect to the frequency with which subjects exhibited significant loss of JSW by dichotomous criteria (i.e., \( \geq 0.5 \) mm; \( \geq 1.0 \) mm; \( \geq 20\% \) or \( \geq 50\% \) of baseline JSW). In dichotomous comparisons based on subjective ratings, a significant difference between treatment groups in the frequency of JSN was seen in gestalt judgments of progression in serially ordered radiographs, but not when the readers were blinded to the sequence of he films. However, progressors and non-progressors,
as defined by each of the dichotomous outcomes, differed significantly with respect to the mean value for quantitative measurements of change in JSW at 30 months ($P\leq0.001$).

**Conclusion:** Although quantitative and semiquantitative indicators of progression of OA in fluoroscopically standardized radiographs of OA knees are highly related, the effect of doxycycline on articular cartilage thickness was more easily detected with quantitative measurements of change in JSW than in semiquantitative ratings of JSN.
The advent of protocols for fluoroscopically assisted positioning of the knee in serial radiographic examinations of patients with knee osteoarthritis (OA) has been lauded as an advance that permits more precise measurements of radiographic joint space width (JSW) – the surrogate for articular cartilage thickness – and more sensitive detection of disease progression than is possible with the conventional standing anteroposterior (AP) view of the knee [1-3]. However, whether precise, quantitative estimates of changes in JSW from standardized knee radiographs are superior to categorical definitions of the progression of knee OA [i.e., as a responder or non-responder, based on loss of JSW beyond the limits of measurement or on changes in semi-quantitative ratings of severity of joint space narrowing (JSN)] has yet to be demonstrated.

We have recently conducted a randomized placebo-controlled trial of doxycycline in subjects with unilateral knee OA. The results of this trial, presented in detail elsewhere [4], indicate that treatment with doxycycline slowed the rate of loss of JSW over 30 months by 33% in the knee with established OA at baseline, compared to placebo. Indeed, the precision of quantitative measurements of JSW obtained from fluoroscopically standardized knee radiographs in this study permitted the detection of a significant effect of doxycycline on the rate of loss of JSW in the index knee within only 16 months. However, doxycycline did not affect the rate of JSN in the contralateral knee [4]. Herein, we compare quantitative measurements of changes in JSW to dichotomous definitions of the progression of JSN in the index knee, based on responder criteria and semiquantitative ratings of the severity of JSN, with respect to their ability to detect a difference between treatment groups in this trial with respect to progression of knee OA.
METHODS AND MATERIALS

The procedures, benefits, risks, and associated safeguards in this trial were approved by the Institutional Review Boards (IRB) affiliated with the 6 participating Clinical Research Centers: Indiana University – Purdue University at Indianapolis, Northwestern University, University of Alabama at Birmingham, Arthritis Research Center Foundation (Wichita KS), University of Arizona and University of Pittsburgh.

Clinical Trial Overview. Subjects were 431 obese women 45-64 years of age with unilateral radiographic knee OA, based on American College of Rheumatology criteria [5]. The eligibility criteria required the presence of Kellgren and Lawrence (K&L) grade 2 or 3 changes in one knee (the index knee) and grade 0 or 1 changes in the contralateral knee [6] in a conventional weight-bearing anteroposterior (AP) view of both knees in extension. All subjects were in the upper tertile of the age- and race-appropriate norms for body mass index (BMI) in women [7]. Two hundred eighteen subjects were randomized to treatment with doxycycline (100 mg twice daily) for 30 months; 213 were assigned to the placebo group. Each subject underwent a series of radiographic examinations at baseline and 16 months and 30 months later, which included a fluoroscopically standardized semiflexed anteroposterior (AP) view of each knee [8]. The standing AP radiograph was repeated at 30 months to determine the progression of overall radiographic severity of OA by K&L criteria [6].

Quantitative Measurement of JSW. The primary outcome measure of the trial was change in JSW in the medial tibiofemoral compartment. Minimum JSW in the medial compartment was measured manually according to the method of Lequesne [9], using the points of a screw-adjustable compass and a graduated loupe. Measurements were obtained from serially ordered radiographs by a reader (SAM) who was blinded to the treatment group assignment of the subject. Measurements of JSW were adjusted for radiographic magnification,
based on the diameter of the projection of a 6.35-mm steel ball, which was affixed to the skin over the head of the fibula during the examination. The intra- and inter-reader reproducibility of measurement of JSW, based on a random sample of 30 radiographs, was excellent (intra-class correlation coefficient = 0.985 and 0.956, respectively) [10].

**Semiquantitative Ratings of OA Severity.** The overall radiographic severity of knee OA (K&L criteria) and the severity of JSN were rated independently by two readers (SAM, KDB) who were blinded to treatment group and to the sequence of the films. K&L grades were determined in the standing AP radiographs obtained at the screening visit and at 30 months. Medial compartment JSN in the semiflexed AP views was rated on a 0-3 scale, based on exemplars in a standard pictorial atlas [11]. Differences between the two readers were discussed until consensus was achieved; if consensus could not be reached, a musculoskeletal radiologist (KAB) was consulted and agreement was reached among the three examiners. After the radiographs had been read with the chronologic sequence of the images masked, the films were unmasked with respect to sequence and the examiners then recorded their gestalt judgment with respect to the progression of JSN between the baseline and 16 month exam, the 16 and 30 month exam, and the baseline and 30 month exam. The reproducibility of semiquantitative ratings of overall OA severity (K&L grade) and severity of JSN was very high (kappa = 0.86 and 0.85, respectively).

**Statistical Analysis.** Because the analysis of primary outcomes in this trial found a significant effect on change in JSW only in the index knee, comparisons of treatment groups with respect to alternative, dichotomous definitions of OA progression in the present study were restricted to that knee. The original comparison of treatment groups with respect to quantitative measurements of change in JSW over 16 and 30 months was performed with a mixed effects linear (i.e. repeated measures) model with the critical value for statistical significance set at 0.05.
The model included a random subject effect and fixed effects for Treatment Group, Clinical Center, Visit (i.e., a class variable with two levels, 16 or 30 months), the Clinical Center x Treatment Group and Visit x Treatment Group interactions and baseline JSW and pain (WOMAC Pain scale [12]) as covariates. Treatment groups were compared at 16 months and 30 months also with respect to the frequency with which the index knee exhibited loss of JSW $\geq 0.50$ mm. This criterion was based on our previous field test of the semiflexed AP radiograph [13], in which we found that the standard error of measurement JSW in repeated semiflexed AP radiographs meeting quality control criteria was 0.25 mm (i.e., 95% confidence interval $= \pm 0.50$ mm). These comparisons were performed using logistic regression analyses with P-values for odds ratios adjusted for baseline JSW and pain.

Logistic regression models were used also to compare treatment groups with respect to three alternative, dichotomous definitions of progression of JSN, based on consensus ratings: First, subjects were designated as progressors at 16 months and 30 months if the atlas-based rating of severity of JSN in randomly ordered pairs of semiflexed AP views increased over time by $\geq 1$ grade, relative to baseline. (Knees with grade 3 medial JSN at baseline were omitted from the analysis). The second definition of progression of JSN was based on the gestalt rating of JSN at 16 months and 30 months in serially ordered semiflexed AP radiographs. The third definition of progression was based on the overall ratings of OA severity (K&L grade) in the standing AP radiograph; progressors were defined as subjects whose index knee exhibited an increase $\geq 1$ in K&L grade. $P$-values for were adjusted for knee pain and the baseline rating of severity of JSN or K&L grade, as appropriate.

To ascertain the level of agreement between semi-quantitative and quantitative measures of JSN, we compared subjects who exhibited progression of JSN, based on dichotomous
definitions, with non-progressors with respect to the mean of quantitative measurements of change in JSW. Comparisons were preformed using Student’s t-test.

RESULTS

Three hundred seven of the 431 randomized subjects (71%) completed the 30-month trial per protocol (149 still taking doxycycline, 158 still taking placebo). Of the 124 dropouts, 60 returned for a semiflexed knee radiograph at 30 months, resulting in an overall rate of loss to follow-up of only 14.8%.

Continuous Change in JSW. The treatment groups were equivalent at baseline with respect to mean JSW in the index knee (Table 1). In the placebo group, the mean of change in JSW (±SD) in the medial tibiofemoral compartment at 16 months was -0.24 ± 0.54 mm; in the doxycycline group, the mean change in JSW at 16 months was 37.5% smaller in magnitude than in the placebo group (-0.15 ± 0.42 mm). At the 30-month examination, the underlying rate of loss of JSW was 33% slower in the doxycycline group than in the placebo group (mean change = -0.30 vs. -0.45 mm). After adjustment for baseline JSW and knee pain, time and clinical center, the difference between treatment groups was significant at both the 16-month and 30-month examinations (P = 0.027 and 0.017, respectively).

Dichotomous Change in JSW. An analysis of the effects of doxycycline on change in medial JSW by dichotomous definitions of progression of JSN, based on continuous JSW measurements, is shown in Table 2. Twenty-nine subjects in the doxycycline group (15%) and 41 in the placebo group (22%) exhibited loss of JSW in the index knee at 16 months greater than the limits of the 95% confidence interval (CI) for measurement of baseline JSW (i.e., ≥0.5 mm). The difference between treatment groups with respect to the frequency of progression of JSN by this definition was not significant (P = 0.173 after adjustment for baseline JSW and knee pain).
By stricter criteria (i.e., JSN ≥ 1.0 mm), the frequency of progression of JSN at 16 months in the doxycycline and placebo groups decreased by approximately two-thirds (4% and 7%, respectively), in comparison with the more permissive definition, but the significance of the difference between treatment groups improved only slightly \((P = 0.117)\). When progression of JSN at 16 months was defined by the per cent loss (e.g., ≥20%, ≥50%) of baseline JSW, the differences in frequency between treatment groups did not approach significance (Table 2).

An additional 14 months of observation did not improve the ability of dichotomous indicators of progression of JSN to reflect the significant effect of doxycycline. While Table 2 shows that all such comparisons between treatment groups with respect to the frequency of progression of JSN at 30 months favored the doxycycline group, none approached statistical significance.

**Semi-Quantitative Grading of JSN.** The effects of doxycycline, as reflected in dichotomous definitions of progression of medial JSN based on semi-quantitative consensus ratings, is shown in Table 3. In these atlas-based ratings, which were made by readers who were blinded to the chronologic order of the radiographs, the frequency of medial JSN in the two treatment groups was similar at 16 months (16-18%) and 30 months (18-22%).

In comparison with the blinded, atlas-based gradings of medial JSN, in which a full 1-point increase in a semi-quantitative scale was required to define progression, gestalt judgments of progression of JSN in serially ordered radiographs detected more subtle changes and yielded much higher rates of progression (Table 3). These judgments indicated a 35% lower frequency of progression of JSN at 16 months in the doxycycline group than in the placebo group (16% vs. 25%, \(P<0.05\)). However, by 30 months, this difference was no longer significant.

**Progression of K&L Grade.** Based upon K&L criteria [6], the frequency of progression of overall radiographic severity of OA at 30 months was 30% in the doxycycline group and 22%
in the placebo group \( (P = 0.188) \) (Table 3). In both groups, approximately 30% of subjects with a K&L grade of 2 at baseline showed progression to grade 3 or 4; among subjects with a baseline K&L grade of 3, 26% in the doxycycline group and 16% in the placebo group showed progression to grade 4.

**Agreement Between Quantitative and Semi-Quantitative Outcomes.** Table 4 contains a summary of the extent of agreement between quantitative and semi-quantitative approaches to defining progression of JSN at 30 months. Among the 86 subjects in both treatment groups who exhibited progression of OA in the index knee by K&L criteria, mean change in JSW (±SD) in the medial compartment was \(-0.64 \pm 0.95 \) mm. In contrast, mean change in JSW among subjects who did not exhibit progression of K&L grade was only \(-0.28 \pm 0.48 \) mm \( (P = 0.001) \). An even greater discrepancy in the mean of quantitative estimates of JSW loss was seen between knees in which blinded, atlas-based ratings of medial JSN were positive for progression and those that did not show progression by this criterion \((-1.05 \pm 0.92 \) mm vs. \(-0.18 \pm 0.42 \) mm, \( P<0.001 \)). Knees in which gestalt judgments indicated JSN also exhibited a greater degree of loss of JSW than knees in which the gestalt judgment did not suggest JSN \((-0.76 \pm 0.94 \) mm vs. \(-0.21 \pm 0.38 \) mm, \( P<0.001; \) Table 4).

**DISCUSSION**

The purpose of the present study was to compare quantitative estimates of change in medial JSW with semi-quantitative ratings JSN and overall OA severity with respect to their sensitivity to detect a difference between treatment groups with respect to the rate of progression of knee OA. As we have reported elsewhere, doxycycline slowed the mean rate of loss of JSW in the medial compartment of the index knee by 33% at 30 months, compared to placebo, and a significant difference between the doxycycline and placebo groups in the rate of loss of JSW was
already apparent in the 16-month JSN data [4]. However, in contrast to its clear effect on quantitative measurements of loss of JSW, doxycycline had no effect on progression of JSN as defined by dichotomous “responder” criteria, based upon longitudinal changes in medial JSW beyond the margin of measurement error. The effect of doxycycline was apparent in gestalt judgments of progression of JSN in chronologically ordered baseline and 16-month radiographs, but not in serial pairs obtained 30 months apart. Neither the frequency of changes in atlas-based semiquantitative ratings of the severity of medial JSN nor the composite grade of overall OA severity (K&L grade) reflected the effect of doxycycline that was apparent in quantitative measurements of change in JSW.

These data differ from the results of previous trials of purported disease-modifying OA drugs (DMOADs) in knee OA. Recent clinical trials of glucosamine [14,15] have yielded radiographic evidence of structure modification in both continuous measurements of change in JSW and in dichotomous definitions of progression of JSN (i.e., change in JSN ≥0.50 mm). Recent placebo-controlled trials of risedronate [16] and intra-articular hyaluronan versus diacerein [17] failed to find a DMOAD effect in either continuous or dichotomous data. However, none of these studies attempted to detect drug effects in atlas-based semiquantitative ratings or of gestalt judgments of JSN.

The data from the present study differ also from the results of the recent ECHODIAH (Evaluation of the CHOndromodulating effect of DIAcerein in osteoarthritis of the Hip) study [18], in which a significant difference between the active treatment group and the placebo group was seen in the frequency of 3-year progression of JSN by a dichotomous definition of progression (i.e., loss of JSW ≥0.50 mm), but not in continuous measurements of change. This difference between the ECHODIAH study and the present study may be due to the substantial (nearly 50%) rate of dropout in the former and the methods used by the ECHODIAH...
investigators to impute missing data. Extrapolation of interim estimates of change in JSW among the dropouts to cover the full 3-year period of the trial resulted, in some cases, in the projection of loss of significant JSW over three years, based on a non-significant change in JSW measured after only one year (e.g., JSN = 0.4 mm after year 1 projects to 1.2 mm after year 3); some projections were made on the basis of even shorter intervals [18]. This procedure may have had a disproportionate effect on the frequency of progression in the placebo group, in which dropouts had more severe OA at baseline and more rapid loss of JSW before discontinuation of study drug than completers. At the same time, the 3-year extrapolation of missing data may have inflated between-subject variability of change in JSW and precluded detection of a significant difference between treatment groups with respect to mean JSN. In contrast, none of the data from the doxycycline trial was imputed.

While published results of DMOAD trials are still rare, numerous teams of investigators have used fluoroscopically standardized knee radiography to detect risk factors for the progression of JSN, as defined by changes in semiquantitative ratings of severity of JSN. These risk factors include varus-valgus malalignment [19], a positive late-phase bone scan [20] and bone marrow edema [21,22]. Indeed, the results of the present study indicate that knees that differ on the basis of dichotomous criteria for JSN exhibit even more significant differences in quantitative measurements of change in JSW (Table 4). While analysis of dichotomous JSN data may better illuminate the formulation of eligibility criteria for inclusion in, or exclusion from, a randomized clinical trial of a purported DMOAD, evaluation of the effects of such drugs can be more powerful if based on continuous, rather than dichotomous, analysis of JSN.
ACKNOWLEDGEMENTS

Data for the doxycycline trial were collected at six clinical research centers: Indiana University Medical Center (John D. Bradley, MD, and Steven T. Hugenberg, MD), the Arthritis Research Foundation (Frederick Wolfe, MD), University of Pittsburgh (Susan Manzi, MD, and Chester V. Oddis, MD), University of Alabama at Birmingham (Larry W. Moreland, MD, and Louis W. Heck, MD), Northwestern University Center for Clinical Research (Thomas J. Schnitzer, MD, and Leena Sharma, MD), University of Arizona Arthritis Center (David E. Yocum, MD).
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Table 1. Baseline joint space width (JSW) in the index knee and quantitative estimates of change in JSW at 16 months and 30 months, by treatment group.

<table>
<thead>
<tr>
<th>TREATMENT GROUP</th>
<th>Placebo</th>
<th>Doxycycline</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean ± SD</td>
<td>N</td>
</tr>
<tr>
<td>Baseline JSW, mm</td>
<td>211</td>
<td>3.61 ± 1.19</td>
<td>218</td>
</tr>
<tr>
<td>Change in JSW at 16 months, mm</td>
<td>191</td>
<td>-0.24 ± 0.54</td>
<td>188</td>
</tr>
<tr>
<td>Change in JSW at 30-months, mm</td>
<td>180</td>
<td>-0.45 ± 0.70</td>
<td>181</td>
</tr>
</tbody>
</table>

* Student’s t-test.
† Derived from a mixed (repeated measures) model with treatment group, clinical center, baseline JSW, baseline knee pain, visit, treatment group x clinical center interaction and treatment group x visit interaction as the independent variables.
Table 2. Frequency of progression of joint space narrowing in the index knee, by treatment group, based on alternative dichotomous definitions of loss of joint space width (JSW), relative to baseline

<table>
<thead>
<tr>
<th>X-ray Exam</th>
<th>Treatment Group</th>
<th>N of Knees</th>
<th>N (%) of Knees with Loss of JSW:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>≥0.5 mm</td>
</tr>
<tr>
<td>Month 16</td>
<td>Doxycycline</td>
<td>188</td>
<td>29 (15)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>191</td>
<td>41 (22)</td>
</tr>
<tr>
<td></td>
<td>Adjusted P-value</td>
<td></td>
<td>0.173</td>
</tr>
<tr>
<td>Month 30</td>
<td>Doxycycline</td>
<td>181</td>
<td>47 (26)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>180</td>
<td>57 (31)</td>
</tr>
<tr>
<td></td>
<td>Adjusted P-value</td>
<td></td>
<td>0.247</td>
</tr>
</tbody>
</table>

*P*-values come from logistic regression analyses and are adjusted for baseline JSW and pain.
Table 3. 30-month progression of Kellgren and Lawrence (K&L) grade and of joint space narrowing (JSN): Consensus of 2 readers who were blinded to treatment group.

<table>
<thead>
<tr>
<th>Indicator of Progression</th>
<th>Doxycycline</th>
<th>Placebo</th>
<th>P§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blind rating of medial JSN at 16 mos*</td>
<td>177 29 (16)</td>
<td>179 32 (18)</td>
<td>0.760</td>
</tr>
<tr>
<td>Blind rating of medial JSN at 30 mos*</td>
<td>171 30 (18)</td>
<td>170 38 (22)</td>
<td>0.285</td>
</tr>
<tr>
<td>Gestalt judgment of medial JSN from 0-16 mos†</td>
<td>187 30 (16)</td>
<td>191 47 (25)</td>
<td>0.046</td>
</tr>
<tr>
<td>Gestalt judgment of medial JSN from 0-30 mos†</td>
<td>181 50 (28)</td>
<td>180 60 (33)</td>
<td>0.249</td>
</tr>
<tr>
<td>Overall radiographic severity (K&amp;L grade) ‡</td>
<td>162 48 (30)</td>
<td>174 39 (22)</td>
<td>0.188</td>
</tr>
</tbody>
</table>

* Increase ≥1 grade of severity of JSN, relative to baseline, based on exemplars from a standardized pictorial atlas [11]. Knees with grade 3 JSN at baseline were omitted from analysis. Radiographs were rated in random sequence.

† Consensus judgment of progression in serially ordered radiographs.

‡ An increase of ≥1 in K&L grade, relative to baseline. Radiographs were rated in random sequence.

§ P-values adjusted for clinical center and, where appropriate, the baseline value for the rating or grade.
Table 4. Change in joint space width (JSW) at 30 months in the index knee, in relation to dichotomous definitions of progression based upon consensus ratings of disease severity.

<table>
<thead>
<tr>
<th>Criteria for Grading Progression</th>
<th>N</th>
<th>Change in JSW, mm (Mean ± SD)</th>
<th>N</th>
<th>Change in JSW, mm (Mean ± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>K&amp;L grade</td>
<td>86</td>
<td>-0.64 ± 0.95</td>
<td>247</td>
<td>-0.28 ± 0.48</td>
<td>0.001</td>
</tr>
<tr>
<td>Medial JSN, severity rating*</td>
<td>68</td>
<td>-1.05 ± 0.92</td>
<td>272</td>
<td>-0.18 ± 0.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestalt judgment of medial JSN†</td>
<td>110</td>
<td>-0.76 ± 0.94</td>
<td>250</td>
<td>-0.21 ± 0.38</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Based on atlas grading of films that were blinded with respect to chronologic order

† Based on the grading of films after unblinding with respect to chronologic order