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REVIEW

Lessons Learned From Nine Clinical Trials of Disease-Modifying Osteoarthritis Drugs

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Introduction

Osteoarthritis (OA) is the most common specific joint disease in humans and the largest cause of chronic disability in the elderly (1–5). Historically, treatment of OA has been symptomatic, with emphasis on control of joint pain and maintenance of function (6,7). Recently, however, reports of clinical trials of purported disease-modifying OA drugs (DMOADs) have been published (8–16). These studies reflect a wide variety of choices by the investigators with respect to selection of the target joint, clinical eligibility criteria, experimental design and procedures, and outcomes representing both structure modification and symptom modification.

The purpose of this analysis is to examine the commonalities and differences among published DMOAD studies and to identify design parameters and procedures that may facilitate or hinder the demonstration of disease modification. To maximize the relevance of this analysis to the design of future studies, we considered only randomized, placebo-controlled trials in which radiographic joint space narrowing (JSN) was utilized as an outcome measure and published protocols for standardizing the radioanatomic position of the joint in serial radiologic examinations, as recommended by authorities in the field, were applied (17). In addition, because it is hoped that objective evidence of structure modification will be accompanied by an improvement in symptoms (18), we examined the effects of the purported DMOADs on joint pain, as described in the reports of the trials.

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Overview of DMOAD trials

Several drugs and nutriceuticals have been evaluated as possible DMOADs and their effects on progression of OA published in the past 4 years. These include orally administered glucosamine sulfate (8,9), chondroitin sulfate (10,11), doxycycline (12), risedronate (13), and diacerein (14,15), and intermittent courses of intraarticular (IA) injection of hyaluronan (15,16). All but 1 trial (12) were sponsored by the pharmaceutical manufacturer.

In trials of glucosamine (8,9) and chondroitin sulfate (10,11), it has been shown that active treatment effectively halted the progression of radiographic JSN and ameliorated symptoms of OA. However, the decrease in mean pain scores in the active treatment groups in most of these studies was smaller than that judged by most patients as being clinically significant (19,20), and recent trials of the symptomatic benefit of glucosamine have failed to replicate these results (21). Furthermore, a recent glucosamine withdrawal trial showed that patients who derived short-term symptomatic benefit from glucosamine were as likely to experience a flare of OA pain while still taking glucosamine as those whose treatment had been switched to placebo (22).

In contrast to the virtually complete arrest of JSN observed in glucosamine and chondroitin sulfate trials, the results of a recent clinical trial of doxycycline suggest that this drug may have a modest effect on the rate of JSN in patients with knee OA (12). While the low severity of knee pain at baseline imposed a floor effect and precluded demonstration of symptom reduction, a post hoc analysis suggested that the doxycycline-induced slowing of the rate of JSN may be accompanied by a decrease in the frequency of exacerbations of joint pain (12). The results of trials of diacerein (14,15) and IA hyaluronan (15,16) offer inconsistent evidence of structure and/or symptom modification. The single published trial of risedronate (13) failed to demonstrate a significant DMOAD effect.

Table 1. Study drugs, design, sample characteristics, and subject retention in randomized, placebo-controlled trials of DMOADs*

	Study design			Sample characteristics				Subject retention	
Drug(s) (ref.)	OA joint	Dosage	Months of treatment	No. of subjects	% female	Age, mean ± SD years	BMI, mean ± SD kg/m^2	% completing	Modified ITT group†
Glucosamine sulfate (8)	Knee	1,500 mg/day	36	E: 106 C: 106	76	66 ± 8	27 ± 3	E: 64 C: 67	NR
Glucosamine sulfate (9)	Knee	1,500 mg/day	36	E: 101 C: 101	78	62 ± 7	26 ± 2	E: 65 C: 54	NR
Chondroitin sulfate (10)	Knee	800 mg/day	24	E: 150 C: 150	51	63 ± 10	28 ± 5	E: 73 C: 73	All: 95
Chondroitin sulfate (11)	Knee	800 mg/day for 3 months every 6 months ×2	12	E: 54 C: 56	81	64 ± 9	NR	E: 80 C: 73	E: 72 C: 70
Doxycycline (12)	Knee	200 mg/day	30	E: 218 C: 213	100	55 ± 6	37 ± 6	E: 68 C: 74	E: 83 C: 87
Risedronate (13)	Knee	5 and 15 mg/day	12	5 mg: 96 15 mg: 90 C: 98	60	63 ± 8	29 ± 4	81	100
Diacerein or IA hyaluronan (15)	Knee	DIA: 100 mg/day HA: 25 mg/week for 3 weeks every 3 months ×3	12	DIA: 85 HA: 131 C: 85	68	65 ± 8	29 ± 5	DIA: 94 HA: 93 C: 94	All: 92
IA hyaluronan (16)	Knee	20 mg/week for 3 weeks every 4 months ×3	12	E: 208 C: 200	68	64 ± 9	30 ± 5	E: 77 C: 80	E: 65 C: 69
Diacerein (14)	Hip	100 mg/day	36	E: 262 C: 259	60	63 ± 7	26 ± 4	E: 50 C: 53	E: 84 C: 87

* DMOADs = disease-modifying osteoarthritis drugs; BMI = body mass index; ITT = intent-to-treat; E = experimental treatment group; C = control (placebo) group; NR = not reported; IA = intraarticular; DIA = diacerein; HA = hyaluronan.
† Percent of subjects for whom at least 1 postrandomization radiograph was available.

Experimental design and conduct of the studies

Table 1 presents a comparison of the studies examined, with respect to subject characteristics, major design parameters, subject retention, loss to followup, and adherence to dosing protocols.

Target population. Consistent with the epidemiology of OA, the large majority of subjects in most of the trials were female. In all but 1 trial, the mean age was >60 years, and mean body mass was in the range considered overweight (body mass index [BMI] 25–30 kg/m^2). The exception was the doxycycline trial (12), in which the sample was composed entirely of women who were, on average, 7–11 years younger and weighed more than the typical subject in the other DMOAD studies. The rationale for choosing this OA phenotype was based on an epidemiologic study of women's health in Chingford, UK, in which Spector et al (23) showed that these characteristics placed subjects at high risk for the imminent development of radiographic changes of knee OA.

The risk profile of the target population can have a profound effect on the underlying rate of progression of OA. This is most clearly seen in data from the doxycycline trial (12) and the British Study of Risedronate in Structure and Symptoms of Knee OA (BRISK) (13), which were of similar duration (24–30 months) and used the identical radiography protocol. In the placebo group in the former, the annualized rate of JSN in the index knee was 0.18 mm. In the placebo group in the BRISK study (13), in which the target population was younger and less obese and included both sexes, the mean annualized rate of JSN over 12 months in the signal (OA) knee was only 0.12 mm. However, while the abundance of risk factors characterizing subjects in the doxycycline trial clearly increased the underlying rate of progression and facilitated detection of a DMOAD effect, the extent to which the homogeneity of the sample in this trial—particularly with respect to obesity—may have decreased the generalizability of the results is unknown.

Lesson 1. The feasibility of a DMOAD trial can be enhanced by selection of subjects based on risk factors for progression of OA.

Lesson 2. Heterogeneity of the sample with respect to sex, age, obesity, and severity of knee OA at baseline does not preclude detection of a DMOAD effect.

Duration of treatment. The duration of treatment in a DMOAD study is not a decision made in isolation. The length of time during which a significant difference between treatment groups with respect to the frequency or rate of OA progression can be expected to accrue is an element of the design that must also take into consideration a priori assumptions about drug efficacy and the rate and variability of OA progression in the placebo group, as well as other design issues (e.g., sample size, precision of outcome measure). While a treatment protocol can be lengthened to offset sample size limitations or unavoidable error variation in outcomes, there are practical limits to the duration of treatment in any clinical trial, beyond which the cumulative effects of attrition and nonadherence to the regimen begin to threaten the validity of results. At a recent workshop on radiographic outcomes in DMOAD trials, it was concluded that technical advances in measures of structural outcomes must permit the demonstration of a DMOAD effect in a sample of practicable size within 2–3 years of treatment (24).

The studies we examined ranged in duration from 12 months to 36 months (Table 1). The 4 studies of only 12 months' duration (11,13,15,16) ended with overall completion rates of >75%. In contrast, trials of 36 months' duration (8,9,14) had the lowest rates of completion per protocol (50–67%). Trials of intermediate duration (24–30 months) had completion rates between these extremes. Regardless of the rate of dropout, in most cases the investigators were able to analyze the structure-modifying effect of the study drug in modified intent-to-treat (ITT) groups (i.e., in groups of subjects in whom at least 1 radiographic examination had been performed after randomization) that represented >85% of all subjects randomized (10,12–15). An exception to this was the 12-month study by Jubb et al of the effects of hyaluronan injection (16): although 78% of subjects completed the hyaluronan trial per protocol, only 67% were included in the modified ITT group. The authors indicated that some subjects were excluded from analysis because their knee radiographs were of poor quality (16).

All studies ≥30 months in duration showed a significant effect on the rate or frequency of progression of radiographic JSN (8,9,12,14). Notably, the effect of doxycycline on JSN in the index knee demonstrated in the 30-month doxycycline trial (12) was already apparent in 16-month outcome data. Moreover, significant DMOAD effects were found in some, but not all, studies of only 12 months' duration (11,16).

Lesson 3. The frequency with which subjects completed the DMOAD trials per protocol is inversely related to the duration of treatment.

Lesson 4. Structure modification can be detected radiographically over an interval as short as 12 months.

Table 2. Radiographic evidence of structure modification*

				Continuous JSN outcome (ITT)					Dichotomous JSN outcome		
Drug(s) (ref.)	OA joint	Radiography protocol	Signal joint(s)	Definition	JSW at baseline, mean ± SD mm	JSN, mean ± SD mm†	*P*	DMOAD effect, %‡	JSN ≥	Frequency of progression, %§	*P*
Glucosamine sulfate (8)	Knee	Standing AP + fluoro	Smaller JSW	Minimum	3.89 ± 1.28	E: 0.07 ± 0.76 C: 0.40 ± 0.84	0.003	83	NR	NR	NR
				Mean	NR	E: 0.06 ± 0.81 C: 0.31 ± 0.92	0.043	81	0.5 mm	E: 15 C: 30	0.013
Glucosamine sulfate (9)	Knee	Standing AP + fluoro	Smaller JSW	Minimum	3.76 ± 1.53	E: −0.04 ± 0.51 C: 0.19 ± 0.51	0.001	121	0.5 mm	E: 5 C: 14	0.050
Chondroitin sulfate (10)	Knee	PA 20° flexion	More symptomatic	Minimum	2.38 ± 0.14	E: −0.05 ± 0.48 C: 0.07 ± 0.56	0.05	171	NR	NR	NR
				Mean	3.02 ± 0.15	E: 0.00 ± 0.53 C: 0.14 ± 0.61	0.04	100	NR	NR	NR
Chondroitin sulfate (11)	Knee	Monopodal AP	Both	Minimum	3.60 ± 1.43	E: 0.04 ± 0.83 C: 0.32 ± 1.11	0.047	88	NR	NR	NR
Doxycycline (12)	Knee	Semiflexed AP + fluoro	K/L 2–3	Minimum	3.63 ± 1.17	E: 0.30 ± 0.60 C: 0.45 ± 0.70	0.017	33	0.5 mm	E: 26 C: 31	0.247
			K/L 0–1	Minimum	3.93 ± 0.88	E: 0.47 ± 0.70 C: 0.41 ± 0.67	0.317	−15	0.5 mm	E: 34 C: 32	0.823
Risedronate (13)¶	Knee	Semiflexed AP + fluoro	JSW 2–4 (1) mm	Minimum	3.00 ± 0.52	E: 0.06 ± 0.25 C: 0.12 ± 0.42	0.275	50	0.75 mm	E: 0 C: 6	0.060
Diacerein or IA hyaluronan (15)	Knee	Standing AP + fluoro	More symptomatic	Minimum	4.56 ± 1.20	All: 0.09 ± 0.55	NR	NR	0.5 mm	DIA: 19 HA: 18 C: 20	0.90
IA hyaluronan (16)	Knee	Standing AP + fluoro	JSW ≥4.6 mm	Mean	5.90 ± 0.95	E: 0.13 ± 1.05 C: 0.55 ± 1.04	0.02	76	NR	NR	NR
			JSW <4.6 mm	Mean	3.45 ± 0.80	E: 0.06 ± 1.00 C: −0.20 ± 1.12	0.16	−130	NR	NR	NR
Diacerein (14)	Hip	Standing PA	JSW 1–3 mm	Minimum	2.29 ± 0.85	E: 0.39 ± 0.75 C: 0.39 ± 0.81	1.000	0	0.5 mm	E: 51 C: 60	0.036

* AP = anteroposterior; fluoro = fluoroscopic; PA = posteroanterior; K/L = Kellgren/Lawrence grade (see Table 1 for other definitions).
† Positive values indicate loss of joint space width (JSW); negative values indicate increase of JSW.
‡ Percent decrease in the mean rate of joint space narrowing (JSN) in the active treatment group, relative to that in the placebo group. This value can be >100% if the mean JSW increases over time in the active treatment group or <0% if the mean JSN in the active treatment group is greater than that in the placebo group.
§ Based on a dichotomous definition of JSN beyond the limits of measurement error.
¶ Group E treatment = risedronate 15 mg/day; data from a treatment group receiving 5 mg/day not included.

Adherence to treatment. The methods used to measure adherence to the prescribed dosing regimen in these studies varied to a great extent. Some relied on self-report and a dichotomous definition of satisfactory compliance (e.g., ≥80% of doses taken) (8,9). Others utilized pill counts (10,11,13,14) or electronic dosing monitors (12) that permitted measurement of adherence as a continuous variable representing the percentage of daily doses taken as directed or the percentage of time during which the subject was "covered" by study drug. The reports of the doxycycline trial (12) and the Evaluation of the Chondromodulating Effect of Diacerein in OA of the Hip (ECHODIAH) study (14) both included data on mean adherence rates, which were >90% among completers in both trials. Investigators in the doxycycline trial also reported adherence in their modified ITT group, in which mean therapeutic coverage (i.e., the time covered by study drug) remained >80% even after inclusion of the intervals during which patients who had withdrawn no longer took study medication (25). The high level of therapeutic coverage in the doxycycline trial may have been due to a prerandomization run-in period that excluded otherwise qualified subjects who were unreliable appointment keepers or who could not achieve 80% adherence (26). However, methodologic and mensural variations among trials in the documentation of adherence preclude meaningful comparisons between studies.

Lesson 5. More rigorous practices for measuring and reporting adherence to treatment regimens in future DMOAD trials are needed.

Structure modification

There is general agreement that preservation of the integrity of the articular cartilage is the most important aspect of OA to be measured in assessing the efficacy of a DMOAD (17). It is further accepted that interbone distance in the plain radiograph is the best available surrogate measure for articular cartilage thickness. In support of that view, double-contrast arthrography has confirmed the accuracy and precision of measurements of radiographic joint space width (JSW) for assessing cartilage thickness in OA knees (27). Even though magnetic resonance imaging findings have indicated that early radiographic JSN in the knee may reflect subluxation or degeneration of the meniscus (28,29), it remains the most widely accepted surrogate for thinning of articular cartilage associated with OA.

Table 2 compares the methods used to document radiographic progression of OA and the effects of the study drug on JSN in the DMOAD trials examined. The ECHODIAH study (14) was the only trial to focus on OA of the hip; in the remainder the effect of DMOAD on knee OA was investigated. To some extent, the preference for use of the knee as the signal joint may reflect the importance of knee OA as a highly prevalent and disabling condition (1–5) and the recent efforts to develop protocols for standardized positioning of the knee during serial radiographic examinations (24). However, Dougados has suggested that the hip, because of the relative ease with which reproducible positioning of that joint may be achieved on serial examinations, may afford greater potential than the knee for demonstration of structural and symptomatic effects of a DMOAD (30,31).

Lesson 6. More clinical trials involving patients with hip OA are needed to determine the more practicable joint in which a DMOAD effect may be demonstrated.

Radiography protocol. The DMOAD trials published to date have tended to utilize fluoroscopy to standardize the radioanatomic position of the knee in serial examinations (Table 2). These studies benefit from the observations in several previous investigations that fluoroscopically standardized alignment of the medial tibial plateau and central x-ray beam in serial examinations facilitates the detection of JSN (32–34). Increased sensitivity to radiographic JSN can benefit the design of a DMOAD trial by permitting the use of fewer subjects per treatment group or a shorter duration of treatment than is necessary with conventional radiographic methods. In some studies, however, the knee was positioned in full extension (8,9,15,16), while in others (10,12,13) a reproducible degree of flexion was sought. In both trials of glucosamine (8,9) and both trials of IA hyaluronan (15,16), fluoroscopy was used to adjust the angulation of the x-ray beam to align it in a parallel manner with the medial tibial plateau (i.e., the floor of the joint space and reference point for measurement of JSW) (Figure 1) before acquisition of a standing anteroposterior (AP) radiograph. In both the doxycycline and the risedronate trials (12,13), the fluoroscopically assisted semiflexed AP view developed by Buckland-Wright (35,36), which positions the knee in 7–10° flexion to achieve parallel alignment of the medial tibial plateau relative to a horizontal x-ray beam, was used.

The data in Table 2 provide ample evidence that fluoroscopically assisted standardization of the position of the knee, either in extension or in some degree of flexion, in serial examinations facilitates the detection of a DMOAD effect (8,9,12,16). However, caution should be exercised when considering whether radiography of

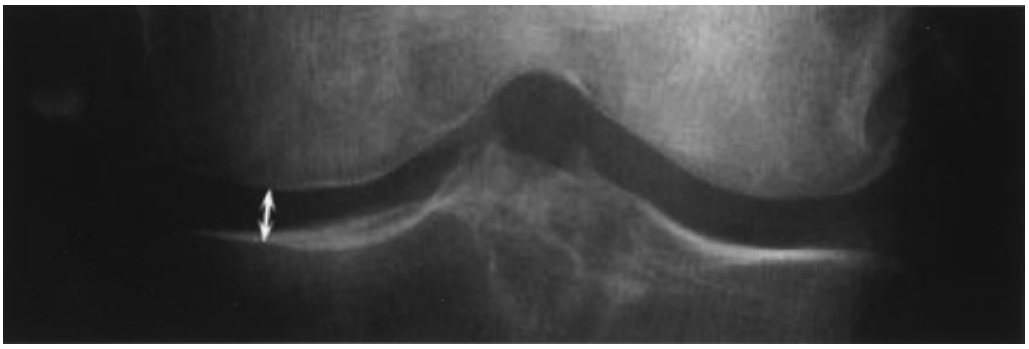

Figure 1. Radiographic image of the tibiofemoral joint space. **Double-headed arrow** indicates the minimum joint space width in the medial compartment, measured between the distal margin of the femur and the "floor" of the joint space, i.e., the dense cortical line representing the medial tibial plateau. To achieve reproducible radioanatomic alignment of the medial tibial plateau in serial examinations, fluoroscopy can be used to adjust the degree of knee flexion relative to the angle of the x-ray beam. Alternatively, the degree of knee flexion may be fixed and the angle of the beam adjusted to achieve alignment.

the knee in extension with weightbearing—with or without fluoroscopically assisted angulation of the x-ray beam—is suitable for a DMOAD study. Messieh et al (37) have shown that 20–30° flexion of the knee provides contact between the femur and the tibia in the posterior aspect of the femoral condyle, i.e., the region in which cartilage damage in OA is usually most prominent. Moreover, the standing AP radiograph may exhibit artifactual changes in JSW due to longitudinal changes in knee pain (38). Although protocols alternative to fluoroscopy, which use empirically derived methods to standardize knee flexion, rotation, and beam angulation, have been developed (39,40), the results of their use in a DMOAD trial have yet to be published.

Lesson 7. Fluoroscopically standardized positioning of the knee, either in extension or in semiflexion, permits detection of a DMOAD effect within 1–3 years.

Lesson 8. A direct comparison of protocols for fluoroscopically assisted standing AP versus semiflexed AP views in the context of a DMOAD trial is needed to ascertain the extent to which the former may be susceptible to artifactual changes due to symptom modification.

Measurement of JSW. All of the studies we reviewed used continuous measures of JSW (Table 2). All but 1 (16) measured medial compartment JSW at its narrowest point (i.e., minimum JSW); Jubb et al (16) estimated the mean, rather than minimum, JSW across the breadth of the medial compartment. Two reports (8,10) included data on both minimum and mean JSW. Previous comparisons of these 2 measurement approaches suggest that they have similar sensitivity to radiographic JSN (32,41). Indeed, in the 2 studies in which a DMOAD effect was evaluated with measurements of both minimum and mean JSW (8,10), significant differences between drug and placebo were observed with both sets of measurements.

The DMOADs with the largest effect on continuous JSN measurements (i.e., those in which the rate of JSN in the active treatment group was slowed by >75% compared with the control group) were glucosamine sulfate (8,9), chondroitin sulfate (10,11), and IA hyaluronan (16). Although the results of the glucosamine trials have been called into question because positioning of the knee for the standing AP radiograph in serial examinations can be affected by longitudinal changes in knee pain in a way that can result in the false appearance of JSN (38), post hoc analyses by the glucosamine trial investigators suggest that changes in pain did not confound detection of JSN in those studies (42). We and our colleagues in a study of patients at 6 centers (12) observed a more moderate effect of doxycycline (33%) on the rate of JSN. In that trial, in which, based on Kellgren/Lawrence grade (43), subjects had unilateral knee OA at baseline as seen on the standing AP radiograph, the DMOAD effect was seen only in the knee with established radiographic OA at baseline; doxycycline had no effect on the rate of JSN in the contralateral knee.

In several studies (8,9,12–15), the analysis of continuous JSN measurements was supplemented with an analysis of the frequency of progression of OA, based on a dichotomous definition of JSN progression. In these analyses, treatment groups were compared with respect to the frequency with which subjects exhibited loss of JSW beyond the limits of measurement error (e.g., the 95% or 99% confidence interval). In the 2

glucosamine trials (8,9), which demonstrated large effects on the rate of JSN, and in analyses in which the null hypothesis was accepted (i.e., for the contralateral knee in the doxycycline trial [12] and in the risedronate trial [13]), the comparison of treatment groups with respect to the frequency of OA progression yielded the same results as those based on continuous JSN data. In contrast, the modest effect of doxycycline on JSN in the index knee was seen only in the analysis of continuous JSN measurements. Notably, the ECHODIAH study failed to demonstrate a significant effect of diacerein on mean JSN in hip OA (14), yet significantly fewer subjects in the diacerein group than in the placebo group exhibited JSN $\geq$0.50 mm. The uniqueness of the ECHODIAH study in this regard is difficult to explain—possibly, a higher rate of attrition in the placebo group and the method used to extrapolate JSN estimates for subjects with missing data served to bias comparisons in favor of the diacerein group.

Lesson 9. Measurements of the minimum and the mean medial tibiofemoral JSW are similarly capable of detecting a DMOAD effect.

Lesson 10. Unless a DMOAD study is designed to detect a large structure-modifying effect, analysis of JSN as a continuous outcome variable is preferable to comparisons based on a dichotomous definition of progression.

Selection of a signal knee. The studies of subjects with knee OA used varying strategies for identifying the knee in which the presence of a DMOAD effect was to be assessed (Table 2). These included selection of the knee with the smaller JSW or more severe pain at baseline (8–10,15), or with baseline JSW within a specified range (13,14). In others, change in JSW in both knees was examined (11,12). Because the rate of JSN appears to increase as JSW decreases (44,45), it has been proposed that disease modification may be more easily demonstrated in joints with relatively more advanced OA than in those with early disease. The positive results in trials that defined the signal knee as the one with greater radiographic or symptomatic severity (8–10) are consistent with this hypothesis. However, 2 trials (12,16) offered direct comparisons of DMOAD effects in knees with differing levels of OA severity.

As mentioned above, doxycycline was found to slow the rate of JSN in the index knee of subjects with unilateral knee OA, but not in the contralateral knee, in which evidence of OA in the standing AP radiograph was absent at baseline (12). In contrast, Jubb et al (16) found that the structure-modifying effect of IA hyaluronan was apparent only in knees in which mean JSW at baseline was $\geq$4.6 mm. Notably, the mean JSN over 12 months in the placebo (saline injection) group in their study was 0.55 mm—larger in absolute terms than that in all other studies of similar or longer duration. This raises the possibility that JSN in the placebo group was influenced by regression to the mean or that increases in knee pain in the placebo group resulted in large, artifactual decreases in JSW seen on the standing AP radiograph (38).

Lesson 11. The weight of evidence currently supports selection of the knee with greater radiographic or symptomatic severity of OA as the signal knee for demonstration of a DMOAD effect.

Symptom modification

A drug that slows the rate of JSN in subjects with OA but does not improve symptoms is unlikely to be accepted as a DMOAD (18). Therefore, the design of a gainful DMOAD trial must also take into account the minimum level of severity of knee pain required at baseline for study enrollment and the means by which to isolate the effects of the active treatment on pain from pain changes due to other sources.

In most of the protocols, patients were asked to rate the severity of joint pain retrospectively over a defined interval, using either the 5-item pain scale from the Western Ontario and McMaster Universities OA Index (46) or single recall questions about either spontaneous or activity-induced pain flares. The doxycycline study (12) measured pain immediately after a 50-foot walk. The most common response format for pain assessments was the 100-mm visual analog scale (VAS). To facilitate comparisons between studies using different pain measures, published results were transformed arithmetically to a range of 0–100 (i.e., as a 100-mm VAS).

Severity of joint pain. A comparison of the trials with regard to baseline levels of pain and the mean and variability of changes in pain scores within treatment groups is presented in Table 3. The studies varied considerably with respect to the severity of knee pain at baseline. Subjects in the chondroitin sulfate study by Uebelhart et al (11) and the hyaluronan-diacerein study by Pham et al (15) reported the highest mean levels of pain at baseline (60 mm). The trial population with the least severe symptoms was the group with unilateral knee OA in the doxycycline trial (21 mm for the index knee and 14 mm for the contralateral knee) (12).

Both trials of glucosamine (8,9), the chondroitin sulfate trial by Uebelhart et al (11), and the trial of hyaluronan by Jubb et al (16) demonstrated a significant

Table 3. Effect of treatment on joint pain*

Drug(s) (ref.)	OA joint	Concomitant pain medications	Assessment procedures			VAS pain score (ITT)		
			Acet./NSAID washout?	Type of joint pain (scale)	Signal joint(s)	Baseline, mean ± SD mm†	Change, mean ± SD mm‡	*P*
Glucosamine sulfate (8)	Knee	No NSAIDs	No	WOMAC (VAS)	Smaller JSW	37 ± 21	E: −7 ± 21 C: −2 ± 19	0.047
Glucosamine sulfate (9)	Knee	Acet. or NSAID	No	WOMAC (Likert)	Smaller JSW	26 ± 13	E: −8 ± 9 C: −5 ± 26	0.03
Chondroitin sulfate (10)	Knee	Acet. or NSAID	No	WOMAC (10-point numerical)	More symptomatic	18 ± 19	E: −2 ± 12 C: −1 ± 12	NS
Chondroitin sulfate (11)	Knee	Acet.	24 hours	Spontaneous (VAS)	Both	60 ± 17	E: −25 ± NR C: −15 ± NR	<0.05
Doxycycline (12)	Knee	An analgesic or NSAID	5 half-lives	After 50-foot walk	K/L 2–3	21 ± 24	E: +2 ± 30 C: +3 ± 23	NS
					K/L 0–1	14 ± 22	E: 0 ± 24 C: +6 ± 24	NS
Risedronate (13)§	Knee	Acet. or NSAID	2 days	WOMAC (VAS)	JSW 2–4 mm	NR	E: −10 ± 32 C: −7 ± 30	NS
Diacerein or IA hyaluronan (15)	Knee	Acet. or NSAID	2–7 days	Spontaneous (VAS)	More symptomatic	60 ± 14	DIA: −34 ± 26 HA: −34 ± 29 C: −35 ± 27	NS
IA hyaluronan (16)	Knee	Analgesic/NSAID	No	Walking pain (VAS)	More symptomatic	54 ± 19	E: −9 ± NR C: −5 ± NR	0.048
Diacerein (14)	Hip	Acet. or NSAID	3–7 days	After physical activity (VAS)	JSW 1–3 mm	45 ± 20	E: −3 ± 30 C: −3 ± 30	NS

*Acet. = acetaminophen; NSAID = nonsteroidal antiinflammatory drug; WOMAC = Western Ontario and McMaster Universities OA Index 5-item pain scale; JSW = joint space width; NS = not significant; K/L = Kellgren/Lawrence grade (see Table 1 for other definitions).
† Results from measures that were not visual analog scales (VAS) were transformed arithmetically to reflect mean and variability within a range of 0–100 mm.
‡ Mean change in VAS pain scores from baseline to end of the double-blind phase.
§ Group E treatment = risedronate 15 mg/day; data from a treatment group receiving 5 mg/day not included.

difference between treatment groups with respect to changes in knee pain. However, only in the chondroitin sulfate trial (11) was the decrease in mean pain score (25 mm) of a magnitude that could be considered clinically significant. Tubach et al (19) have shown that a 19-mm decrease in a VAS pain score corresponds to the minimum decrease in pain severity rated as satisfactory by <75% of OA patients. However, among patients in the upper tertile of pain scores at baseline (who were more similar to those studied by Jubb et al [16]), the minimum clinically important improvement found by Tubach et al was larger (i.e., 36.6 mm). This much larger value may reflect a higher threshold for appreciating relief of symptoms among patients with high levels of pain. Alternatively, the fact that the 25-mm decrease in mean pain scores in the active treatment group of the chondroitin sulfate study (11) was only 10 mm greater than that in the placebo group suggests that the symptomatic benefit of chondroitin sulfate in that trial may have been exaggerated by the placebo response and/or regression to the mean.

The mild level of knee pain reported at baseline by subjects in the doxycycline trial (12) left little room for improvement (Table 3). In light of this "floor effect," it was shown in a post hoc analysis that clinically significant increases in knee pain were significantly less frequent in the doxycycline group than in the placebo group.

Lesson 12. Demonstration of symptom modification is facilitated by enrollment of subjects with knee pain of at least moderate severity.

Use and washout of concomitant OA medications. The studies we examined differed from one another in two procedural respects concerning the demonstration of symptom modification. First, they differed with respect to the use of concomitant analgesic and nonsteroidal antiinflammatory drugs (NSAIDs). Most were relatively permissive, while in the chondroitin sulfate study by Uebelhart et al (11), concomitant treatment was restricted to acetaminophen. This may account, at least in part, for the fact that this study had the lowest completion rate among trials of ≥12 months duration.

The second aspect of pain assessment in which studies differed concerns washout of concomitant pain medications; in only 5 of the 9 studies (11–15) was a washout of all NSAIDs and/or analgesic agents required before assessment of joint pain. Among these, the chondroitin sulfate study by Uebelhart et al (11) was the only one to show a difference between treatment groups of ≥10 mm with respect to change in mean VAS pain scores. In contrast, in the glucosamine studies (8,9), in which no washout was required, much smaller differences between treatment groups (3–5 mm) with respect to mean change in VAS pain were observed. The effects of concomitant medications may have obscured a larger effect of glucosamine on joint pain. Although differential efficacy of purported DMOADs with respect to relief of pain cannot be discounted, the detection of symptom modification appears to be facilitated by washout of all concomitant pain medications.

Lesson 13. A liberal policy concerning use of concomitant OA pain medications will decrease the rate of dropout.

Lesson 14. Failure to wash out the effects of analgesic agents/NSAIDs prior to pain assessment may obscure the symptomatic benefit of a DMOAD.

Conclusion

This group of 9 studies, which represents the best available evidence of the feasibility of disease modification in OA, is too small to permit robust conclusions about the disease-modifying properties of any of the drugs studied. However, as a whole, these studies suggest that pharmacologic structure modification in OA is feasible and can be demonstrated using available methods and procedures. Because this body of evidence is so early in its development, it is too soon to speculate on the extent, if any, to which these findings reflect publication bias or a possible lack of objectivity due to industry sponsorship. The 9 trials demonstrate a full range of positive and negative results. As in any area of investigation into therapies, as positive and negative evidence of the efficacy of purported DMOADs continues to accumulate, it will become increasingly possible to ascertain the likely benefit to patients of treatment with a DMOAD, relative to the risks of the drugs themselves and to possible biases in published research. Meanwhile, the implications of greatest value from these early studies lie in the lessons they provide relative to the design and conduct of future DMOAD studies.

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