Structure modification in knee osteoarthritis: methodology and outcome parameters
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Summary
Managing osteoarthritis (OA) with structure-modifying agents (SMAs) is an important emerging topic receiving increased attention from both lay individuals and health care professionals as a promising alternative in the management of OA.

Objective: To review the methodology and outcome parameters purported to be used in the assessment of the structure-modifying potential of various interventions.

Design: A Medline search was performed to select the relevant published articles. This review does not go into detail about various aspects of the design and conduct of structure-modifying studies; however, a vast number of relevant references are provided and may be accessed by interested readers.

Results: Enhancing the feasibility of SMAs trials aimed at documenting efficacy can be accomplished by carefully selecting: (1) the outcome parameters, (2) the imaging methodology, and (3) the patient population. Most of the relevant issues that need to be considered by investigators before embarking on a study of this nature have been addressed in this article.

Conclusion: Most of the evidence to date focuses on the superiority of the radiographic-based techniques in measuring joint space narrowing among a homogeneous population of OA patients. More research is warranted before other techniques such as ultrasound, chondroscopy, and magnetic resonance imaging, can be proven to be reliable. © 2001 OsteoArthritis Research Society International

Key words: Knee, Osteoarthritis, Cartilage, Joint space, Structure modification.

Introduction
Osteoarthritis (OA) is the most prevalent chronic joint disorder in the U.S.A. and in the world. Lawrence et al. estimated that nearly 21 million Americans had clinical symptoms and signs of OA in 1990. The fact that OA is symptomatic in only half of the patients with radiographic OA emphasizes the magnitude of the problem. The burden of OA disability and dependence among older Americans is second only to chronic heart disease as the primary diagnosis leading to adults receiving Social Security Disability payments. The extent to which OA afflicts Americans is reflected in the cost for diagnosis and treatment. Summarizing data from several studies, Yelin estimated the cost of OA in the US at $15.5 billion (in 1994 dollars). In addition, the disability and medical care costs associated with OA will continue to escalate as the average life expectancy increases to 83.1 years for women and 75 years for men by the year 2040.

The knee joint is a frequently involved joint in OA with great social cost and disability. This article will highlight various aspects related to the structure modification research on knee joint OA, since the majority of the literature on radiographic progression of OA is based on studies of OA of the knee with follow up periods that ranged from 3 to 12 years. To enhance the feasibility of structure-modifying agents (SMAs) trials aimed at documenting efficacy, two important issues must be addressed. The first is reducing the variability of the outcome measurement and the second is shortening the required length of such a trial. Researchers can accomplish these objectives by carefully selecting: (1) the outcome parameters, (2) the imaging methodology, and (3) the patient population.

Outcome parameters and imaging methodology
The need of a reliable method for the evaluation of putative structure-modifying agents has led to a variety of different clinical, imaging and laboratory investigations. These will be discussed separately in the following section.

CLINICAL PICTURE
OA has both clinical and radiographic criteria. The American College of Rheumatologists’ classification criteria for OA has introduced some measure of standardization, but they are not diagnostic criteria. Based on these criteria, for clinical study purposes, OA has two main clinical outcomes, pain and functional disability. Tools to evaluate these outcomes have been developed and validated. For example, an algofunctional index of severity for OA of the knee (ISK) was developed by Lequesne et al.
and was validated over five years comparing it with other assessment tools. Other tools proposed to be particularly valuable in providing information on the long-term natural disease course expected with SMA trials. Another tool is the Western Ontario and McMaster Universities (WOMAC) OA index. This is a tri-dimensional, disease-specific health status measure that probes clinically important, patient relevant symptoms in the areas of pain, stiffness and physical function. It is important to note that neither the WOMAC nor the ISK allow separate evaluation of the two knee joints. To help in determining which joint is the symptomatic one, a visual analog scale of pain could be used. Alternatively, the information in the pain subscale of the WOMAC can be collected for each knee separately.


Methods proposed for evaluating radiologic progression of OA include semi-quantitative assessment of individual radiographic features such as marginal osteophytes, JSN, subchondral sclerosis, and malalignment. Others suggest composite indices such as the Kellgren and Lawrence grading and a JSN weighted scale. Still, other researchers applied strictly quantitative measures employing both automated and non-automated methods of joint space width (JSW) measurements. Physicians generally use imaging to confirm the clinical diagnosis of OA, assessing changes in articular cartilage either directly or indirectly. Radiological JSN is considered the most reliable available marker for the assessment of OA progression in SMA clinical trials. In support of this, Ayral et al. and Blackburn et al. reported that articular surface lesions as detected by arthroscope always accompanied JSN on plain radiographs.

Using standardized protocols to obtain reliable radiographic images of joints in the weight-bearing position is crucial in determining articular cartilage loss in the knee. Reliability means the reproducibility of the quantitative measurement of the JSW, i.e. the degree to which repeated measurements of JSW by the same observer, or by different observers, produce highly correlated estimates of JSW. Two parameters are used in the literature to describe the reproducibility of repeated measurement of the JSW. The first one is the coefficient of variation (CV). CV is the ratio of the standard deviation to the mean of the measurement. The lower the CV, the more reproducible it is. The latter is preferred although not reported often in the literature.

Several factors play an important role in the reliability of the radiologic measurement of JSW: imaging procedure, patient positioning, and measurement method.

**Imaging procedure**

Currently, researchers take measurements of radiographic features from both standard and microfocal radiographs. The difference between these two types of radiographs is the size of the X-ray source, which is considerably smaller for the microfocal technique. The advantages of the smaller source are high magnification, high spatial resolution and minimum penumbral blurring i.e. the radiographic margins of features are sharply defined. However, the small source of X-ray results in longer exposure time as it limits the output of the X-ray tube. Nevertheless, patient exposure time and the level of exposure is still within acceptable clinical parameters. The microfocal radiographic equipment is not widely available at present, but the cost is similar to that of a conventional X-ray machine, so expense is not an impediment to implementing this superior technology with regard to a trial in only one center. On the other hand, in a multi-center study the cost will be an issue because the microfocal X-ray is not useful for common radiographs in daily practice.

**Patient positioning**

Lynch et al. and Conrozier et al. established that even small changes in X-ray beam or joint position can dramatically alter the measurement for JSW in the knee and hip joints. If clinicians do not specify their preferences when ordering films, some patients may have X-rays taken in the lying position while others will be standing. Moreover, X-ray technicians may have their own idiosyncratic methods for positioning patients, especially those patients with pain and difficulty in standing or walking.

Ravaud et al. reported that a deviation in foot rotation by as little as 15°, may result in significant variation in the measurements of JSW. In addition, the position of the center of the joint, i.e. the joint space, relative to the central ray of the X-ray beam is crucial as it influences the

RADIOGRAPHIC ASSESSMENT

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magnification of the radiograph image. About a 17% decrease in JSW was observed when the X-ray beam was displaced by 1 cm below its original alignment centered at the mid-point of the patella. The positioning of the center of the joint can be influenced by factors such as obesity and restriction of joint movement. Buckland-Wright et al.49 affixed a magnification marker (a 5-mm ball encased in plexiglass) with tape to the skin overlying the head of the fibula to correct for the degree of magnification. This was after the investigators reported a variation in magnification of the JSW ranging from 9 to 35%. Thus, it is not surprising that in SMA trials, failure to correct for this variability has significant negative implications on the study power therefore necessitating larger sample sizes.29

Another pertinent aspect of positioning is the degree to which the knees are flexed. Ravaud et al.53,60 reported that up to a 12.5% variation in tibio-femoral JSW measurements occurred when they repeatedly radiographed normal knees manipulating knee flexion by as little as 5°. The guidelines published by the Task Force of OA Research Society International29 described two different protocols for radiography of the knee OA. In one, the patient stands with the knees fully extended, while in the other, the patient stands with the knees semi-flexed.43,49,53,57,58 The fully extended position is fraught with errors because cartilage loss is not even throughout the joint. Frequently articular cartilage is spared at the anterior margin of the tibia even when there has been considerable loss from the central articular region in the tibial plateau at the point of weight transmission. Consequently, joint space measurements in the medial compartment of such knees provide an inaccurate measurement of the extent of cartilage preservation, usually overestimated.60

In the standing semi-flexed view each knee is radiographed separately to overcome the differences in the required degree of flexion between the left and the right knees. Each knee is flexed until the medial compartment of the tibial plateau is horizontal relative to the floor of the room and parallel to the central ray of the X-ray beam. In this position, the femoral condyle occupies a postero-central position on the articular surface of the tibia. This position coincides with the site of principle load across the joint during its normal function.61, Messieh et al.49 confirmed that this is the site at which arthroscopy has revealed the highest prevalence of articular cartilage destruction. Therefore, it is not surprising that the standard deviation of JSW measurements taken on knees filmed using the standing extended view was found to be 2.0 mm,60 while Buckland-Wright et al.53 using computerized measurements of JSW and the semi-flexed view, reported standard deviations between 0.5 and 0.79 mm.

**Measurement method**

Examiners can obtain measurements of JSW either manually or using a computer. Lequesne61 described a standardized method of manual measurement of JSW (chondrometry). Several specialized edge-detection computer software applications have been developed to measure JSW in digitized radiographic images.53,62–64. Mazzuca et al.65 concluded that the poor reproducibility of measurements of JSW, the slow rate of OA progression, and the practicalities and cost of clinical trials precluded the use of the conventional radiographic technique using manual measurements of JSW in SMAs trials. The authors clearly showed that the use of computerized measurement of JSW using films taken in the semi-flexed position is expected to reduce the required sample size by 44%. This smaller sample size will allow reductions in patient recruitment, screening and post-randomization costs.

Buckland-Wright et al.49 used a specially prepared computer program for tibio-femoral joint space analysis, measuring the interbone distance at 300 points across the compartment and selecting the narrowest point, the minimum JSW. Using a standard radiograph of the knee in the semi-flexed position, they reported coefficients of variation (CV) for repeated measurement as low as 1% for the medial and 1.5% for the lateral compartments.

Another method that was proposed is the mean JSW. Although the minimum JSW could be more sensitive to pick changes in cartilage than the mean JSW, the latter is less susceptible to the influence of the variation in both radiographic procedures and patient positioning and remains possible when the interbone distance is very small.66 Therefore, some authors suggested the measurement of both parameters, minimum JSW and mean JSW in SMAs trials.67

**Commentary**

In summary, Buckland-Wright et al.49 and Buckland-Wright50 clearly show that the precision and accuracy of JSW measurements are best maximized by fulfilling several parameters; (1) measuring the minimum JSW in the tibio-femoral medial compartment, (2) using computerized measurements, (3) correcting for radiographic magnification, (4) obtaining standard radiograph of the knee in the standing semi-flexed view, and (5) using microfocal radiography.

Unfortunately, the precision associated with the level of standardization used in Buckland-Wright’s technique comes with certain costs represented in the need for special training of investigators in radio-anatomic positioning, use of fluoroscopy and image digitization with specialized computer software and hardware. In addition, the technique is highly technician dependent even after training. According to Mazzuca et al.65, high inter-investigator reproducibility of radio-anatomic positioning of the knee still needs to be established. Furthermore, microfocal radiography of joints is not widely available in clinical radiology departments in the US and consequently this technique could not be easily employed in a multi-center study.65

Perhaps pressured with the logistical limitations of the fluoroscopic-based technique, Buckland-Wright et al.68 conducted a comparative study of three non-fluoroscopic radiographic views: standing extended, semi-flexed, and schuss. The study showed that, radioanatomically, knees in the semi-flexed view were significantly more accurately positioned than in the schuss view, which in turn was better than the extended knee view. Furthermore, joint repositioning and reproducibility of JSW were significantly better in the semi-flexed view than in the other two views.

In this context, it is important to note that there are other limitations of the radiographic assessment of JSW in general. First, radiographs cast a two-dimensional image of a three-dimensional structure on a flat receptor. This allows large portions of the anatomy to be depicted as a single image. This is associated with a superimposition of overlapping structures potentially obscuring structural abnormalities. Second, it is difficult to compare the size of joint spaces between patients especially when the actual radiologic magnification is unknown. For this reason,
appropriate analysis of results would present data as the percentage of change relative to each patient’s baseline film.

Finally, even with the best techniques, radiographs were found to underestimate the extent of cartilage damage when compared to arthroscopy.

MAGNETIC RESONANCE IMAGING

MRI has the potential to provide high quality images of soft tissue allowing visualization of the anatomy and its pathology. MRI is unique in being able to directly visualize all components of the joint simultaneously. This capability allows the examiner to study the entire organ, and places OA in the accurate context of a disease of organ failure. Buckland-Wright published a review of the differences among radiography, arthroscopy and MRI. He concluded that MRI is more sensitive than radiography for detecting OA joint characteristics and is unique in assessing soft tissue changes. In particular, the fat-suppressed three-dimensional spoiled gradient-echo (SPGR) MRI was found to be faster and significantly more sensitive than the standard MRI technique in detecting hyaline cartilage defects. The SPGR further achieved excellent reproducibility among readings and between readers. This technique is widely available and easy to perform using any high-field MRI scanner in clinical use.

On the other hand, some studies report moderate correlation between MRI and arthroscopy in detecting certain cartilage lesions. Early grade 1 subchondral sclerosis and early changes, particularly in articular cartilage, were difficult to detect using MRI. Others suggested that an MRI scoring system is still required and the ability of an MRI to precisely measure changes in cartilage thickness over time in a large joint, such as the knee, has not been sufficiently validated. The total volume of cartilage readily assessed by the MRI offers limited information about the distribution of cartilage changes in the OA joint and consequently is insensitive to focal changes. In addition, its use is difficult in multi-center trials because of the high cost of the MRI machines and the need for highly skilled and specially trained readers.

ARTHROSCOPY

Arthroscopy permits direct magnified visualization of the articular cartilage and is thus very sensitive in detecting surface cartilage defects. Chondroscopy is a simplified technique of arthroscopy. The procedure can be performed with a small arthroscope, under local anesthesia, in an outpatient setting. According to Ike and O’Rourke, using this technique enables investigators to assess as much as 90% of the articular surface. A scoring and grading system proposed by the committee of the French Society of Arthroscopy has been found to have high reliability and low interobserver variation. Unfortunately, arthroscopy does not allow the assessment of softening and thickening of cartilage or changes in the juxtaarticular tissues. Furthermore, the procedure is invasive, subjecting the patient to a variety of risks, and unlikely to be used for frequent follow-up assessment. However, it may have a role in establishing comparative criteria for MRI or other imaging techniques.

ULTRASOUND

Ultrasound is an appealing approach because of its ease of performance and low cost. Its ability as a method of detecting cartilage damage was first studied by Aisen et al. who were able to show significant reduction in cartilage thickness in patients with knee OA compared to normal subjects. Ultrasound was further studied by Myers et al. reporting high accuracy and reproducibility of measurements of the thickness and surface characteristics of normal and OA articular cartilage. Several authors have suggested the use of ultrasound as an evaluative method for cartilage lesion progression during and after OA therapy. Pipitone et al. used ultrasound to document that knee OA patients treated with chondroitin-sulfate maintained articular cartilage as compared to the control group.

However, ultrasound relies on the examiner moving the transducer in a steady manner. Orienting the images properly requires knowing the exact positioning of the transducer relative to a given anatomy. In addition, many areas remain inaccessible because of the overlying bone. These factors render ultrasound highly examiner-dependent and time consuming. The sensitivity of this technique in documenting pathologic changes in OA requires further evaluation.

BIOLOGIC MARKERS

Biologic markers reflect the ongoing dynamic metabolic processes in joint tissues such as cartilage, synovium and bone. Because the ability to sample and monitor these tissues is limited, synovial fluid, blood and urine are currently the only windows to the pathologic processes taking place in the joint. Cartilage oligomeric matrix protein (COMP) and collagen II C-propeptide are examples of markers detected in synovial fluid. Other candidate markers for OA may be found in one or more body fluids. Hylauronate epitopes shown to reflect de-novo proteoglycan synthesis (e.g. 846, 3B3) are examples of markers detected in synovial fluid. Other candidate markers in this application is limited to rheumatoid arthritis. Several authors suggest that in order to remedy this, researchers should collect samples of body fluids in future OA clinical trials to help validate various markers.

There are several applications for biologic markers suggested by researchers. Some of these applications include being used as a diagnostic test for OA; as an evaluative test for severity or staging of OA; as a prognostic test to identify patients more likely to show rapid progression of OA; as a diagnostic test to identify patients more likely to show rapid progression of OA; and as a surrogate outcome measure in clinical trials of SMAs. Unfortunately, the goal of using these markers in assessing the disease process of OA during clinical trials has not been reached. To date, the use of biologic markers in this application is limited to rheumatoid arthritis. Several authors suggest that in order to remedy this, researchers should collect samples of body fluids in future OA clinical trials to help validate various markers.

Notwithstanding the wide array of suggested benefits, the role of biologic markers in OA is still under investigation and there exist several challenges to determining their usefulness.

(1) The concentration of markers in these fluids may depend not only on the dynamics of the disease process but also on such factors as the rate of elimination or clearance from the sampled body compartments and the amount of cartilage remaining in the joint. For example, even...
low-grade synovitis was found to increase synovial clearance.

(2) Treatment with non-steroidal antiinflammatory drugs and corticosteroids might decrease the volume of joint effusion, increasing marker concentration or inhibiting the production of some markers.

(3) The specific source of the marker is difficult to discern both on the level of the tissue and the level of the metabolic process. This issue is even more pertinent when serum or urine samples are assayed. One problem is that not all markers are studied for their relative specificity for both degradative and synthetic events. An increase in the level of a specific cartilage matrix marker could reflect either an increase in degradation or an increase in new synthesis. Another problem occurs when a given fragment of matrix molecule, proposed to be used as a marker, is not present in more abundance in cartilage than in any other joint tissue. For example, the total mass of COMP in the menisci of a knee may approach that in the joint cartilage of the knee.

(4) Changes in lymphatic and hepatic function will affect the clearance of cartilage markers from serum as these organs are responsible for elimination.

(5) There is considerable overlap between OA patients and those in control groups. Possibly this is because serum and/or synovial fluid concentrations of some markers are influenced by age and gender by change in physical activity, or simply by circadian variations.

(6) Methodological limitations of the available data can interfere with the interpretation of findings, e.g. data collected from cross-sectional studies. The manner in which patients are grouped reportedly significantly affected measurements. Hence, careful patient characterization is needed to increase the value of markers.

Another important methodological challenge is assay methods. Assay sensitivity varies according to whether the antibody used is monoclonal or polyclonal, and variations exist between one kit and another.

For these reasons, identification of a single biological marker seems to be an unrealistic goal. Using a combination of several markers might eventually provide better information on the various stages of the pathological process of OA. Further research is still warranted before this approach proves beneficial in the context of SMA trials.

**Patient selection in SMA trials of knee OA**

**HOMOGENEOUS POPULATIONS**

The variance of JSN has two components: measurement error in the assessment of JSW and biologic variation in rate of OA progression. Measurement error is expected to decrease the correlation among repeated measurements of JSW consequently reducing the study power. Reducing measurement error can be attained by selecting appropriate standardized method of measuring JSN as discussed earlier. Reducing the biologic variation can be achieved by studying a ‘homogeneous’ patient population. Inevitably, this might limit the generalizability of the results, but the practical limitations in current imaging and analytical methods make other choices unrealistic. Therefore, it is not surprising that many authors advocate the use of homogeneous populations of patients.

**SOURCE OF PATIENTS’ RECRUITMENT**

A possible source of biologic variation stems from the fact that the progression among patients in the general elderly population suffering from OA, who are likely to be identified by community-based recruitment, may be slower than that in a clinic-based population of patients. Among a group of 252 knee OA patients referred to a hospital, Ledingham et al. found that the majority had bilateral OA affecting more than one compartment of the knee, suggesting a more advanced disease state. Therefore, it was suggested to stratify participants by recruitment source during their randomization to treatment groups. This may assist with balancing the potential differences in the rate of JSN.

**LENGTH OF FOLLOW UP**

Because of problems such as a high rate of dropping out, it is preferred to follow large numbers of patients for shorter periods rather than fewer patients for longer periods. On the other hand, for the vast majority of patients, the mean joint space will diminish with time. Thus, the longer the period of observation, the smaller the variability of JSN in relation to the mean, which increases the study power. A fine balance should be attempted for this trade-off between the number of patients and the length of follow-up. Some investigators have suggested a 2-year follow-up period for these studies to be able to demonstrate radiologically significant improvement in OA. Unfortunately, the optimal follow-up duration in SMAs trials has not been agreed upon; therefore, clinical trials should establish this duration based on both previous data and the characteristics of the studied populations.

**RATE OF OA PROGRESSION**

While the rate of OA progression is variable over time in the same patient and between patients, estimates of the rate of medial tibio-femoral JSN among knee OA patients do exist in the public domain. The estimated annual rate of JSN ranged from 0.06 mm/year to 0.60 mm/year. The likely reason for this 10-fold variation are the differences between the studies in both patient characteristics and methodological features. This finding supports the notion of using a homogeneous population of patients as noted earlier.

Currently, there is little known about the factors controlling progression of OA. Knowledge of these factors would have a huge impact on the design of SMA trials, tremendously increasing the study power. Several studies have suggested criteria for selecting patients more likely to show rapid progression including biological markers in the serum, imaging procedures such as scintigraphy and epidemiological findings. These studies will be addressed briefly in the following section.

**Biological markers**

Sharif et al. studied the prognostic value of serum hyaluronic acid (HA) levels in relation to OA of the knee. They followed 94 patients for 5 years. Patients whose OA had progressed were found to have had significantly higher levels of serum HA at baseline, compared with those whose OA had not progressed.
Spector et al. examined the relationship between low-level increase in serum C-reactive protein (CRP) and the progression of OA. They studied 105 knee OA patients for 4 years and found levels of CRP significantly higher in those that progressed radiographically than in other patients. CPR production is stimulated by cytokines, particularly interleukin-6, and the investigators interpreted their findings as unequivocal evidence of a chronic low-level activation of the cytosine cascade reflecting tissue-damaging process within the joints. However, it is premature to advocate using such markers to choose target patient populations. Further research is warranted to verify the findings of these studies. Other methodological challenges faced when using biologic markers were discussed above in a previous section.

### Bone scintigraphy

A number of groups have used scintigraphy to study the relationship between isotope (technetium-labeled diphosphonate, 99 mTc) retention and radiologic indices of OA severity. They showed a significant correlation between scintigraphic bone scan abnormalities and biologic markers of bone turnover in synovial fluids and suggested that scintigraphy may serve as a predictor of subsequent progression in OA. Dieppe et al. verified this notion by reporting that 88% of the knees with severe scan abnormalities at baseline showed JSN, whereas none of the knees without scan abnormalities showed JSN by the end of 5 years. These findings might be perceived as valuable in the design of SMA trials in that negative scan informs investigators that OA is unlikely to progress over the next few years and that a particular patient is not an ideal candidate for a particular SMA trial. However, the main drawback is the impracticality of implementing this approach. Scintigraphic bone scan is not done routinely for OA patients and is prone to pose a logistical challenge for recruitment of ‘eligible’ patients.

### Epidemiological studies

There have been several epidemiological studies conducted to ascertain predictive factors for the progression of OA. For example, data from Chingford, U.K., suggest that 50% of obese, middle-aged women with radiographic evidence of unilateral knee OA may develop OA in the contra-lateral knee within two years. Therefore, this group is considered at high risk for rapid progression of OA, making them desirable for SMA trials. Other risk factors for OA progression include advanced age, especially among women, coexistence of crystalline diseases, concurrent OA in multiple joints and neuropathy. Patrick et al. reported association between calcium pyrophosphate dihydrate (CPPD) in synovial fluid and higher mean scores for arthritic changes including joint space loss. Another study reported that JSN was associated with worsening symptoms and function, clinical inflammation (effusion and warmth) and the presence of CPPD in synovial fluid. To avoid hampering the efforts of recruitment of patients, it would be advisable to try to satisfy as many of these risk factors as possible rather than restricting the study population to fulfill a specific risk factor.

### CONCOMITANT THERAPY

It is worthwhile noting that the use of rescue medication would influence the drop out rate in clinical trials of SMAs. In two long-term studies, only 57% and 35% of the randomized study subjects completed the 2 years’ duration of these studies. These findings favor providing symptomatic ‘rescue treatment’ as part of the study protocol as it appears that most of the withdrawals in these studies were due to a lack or delay of symptomatic relief. It is important to emphasize that studies of putative SMAs might be ethically compared to placebo if supplemental acetaminophen or NSAIDs are allowed to control symptomatic exacerbation, because at this time no agent can be taken as a benchmark for the treatment of OA. However, in considering rescue medications, special attention should be given to indomethacin because of its potential detrimental effect on cartilage.

### TARGET COMPARTMENT OF THE KNEE JOINT

The knee joint is a complex articulation that can be regarded as having two functionally distinct compartments, the tibio-femoral (TF) which is further separated into the medial and lateral aspects; and the patello-femoral (PF) compartment. Determination of which compartment is affected in OA can be difficult and is highly dependent on the radiographic view. Pathologic studies indicate that OA in the knee joint is heterogeneous in terms of its sites of involvement and that these sites may be affected independently. The extent to which this may occur radiographically has been illustrated in clinical series and in a community survey. These studies found the most common patterns of localization of OA within the knee to be medial TF (45%), followed by PF (35%), and demonstrated that each of these is independently associated with substantial pain and disability. Furthermore, the relative contribution of mechanical and constitutional factors in the pathogenesis of OA in different compartments of the knee joint might vary. Even clinically, a questionnaire like the ISK was validated only for TF OA because OA in the PF compartment is too irregular in pain and severity and it is not a good ‘model’ for trials. Therefore, it has been suggested that clinical trials should not include a mix of patients with TF and PF knee OA, rather they should be treated as separate disorders.

In a study by Buckland-Wright et al., the JSW in the lateral TF compartment remained similar to that of non-arthritic joints. This might account for the radiographically observed lower frequency and severity of cartilage loss in the lateral TF compartment. Moreover, in the Chingford study, the intra- and interobserver reproducibility of the radiographic quantitative measurement of the medial TF compartment was found to be much better than the lateral TF compartment. In another study, Wada et al. found that the positive predictive value of JSN in the medial TF compartment of the knee for the presence of abnormal articular cartilage by the arthroscopy was high (98%), while it was poor in the lateral TF compartment (20%).

Equally important is the choice of the target knee when the OA is bilateral. Clinically, many investigators would ask the patient to identify the most symptomatic knee and label it as the ‘study knee’. However, the radiographic picture is not as straightforward. The dilemma stems from the pool of significant association between the clinical and the radiographic changes in OA as noted earlier. The current recommendation is to measure the JSN bilaterally even if the contralateral involvement is asymptomatic.
SEVERITY OF DISEASE

A SMA is expected to demonstrate more efficacy in OA joints that have mild to moderate pathology than in joints with severe disease. In experimental animals, when treatment began before histologic changes in cartilage started, the severity of OA was remarkably reduced. On the other hand, JSN accelerates with OA severity, which increases the study power as discussed earlier. Therefore, a fine balance should be sought between recruiting patients with mild enough OA to show efficacy of the studied SMA, and at the same time are severe enough to guarantee a reasonable rate of OA progression. Such formula might be found among patients with several years' duration of OA, rather than in newly diagnosed patients.

Clinically, pain is considered to be the most important symptom and consequently the most important outcome measurement, but it is not yet clear what minimal frequency and severity of pain should be required for entry to SMAs trials. Perhaps a minimal clinical level, similar to that which is well justified for symptomatic studies to provide a ‘room’ for improvement, may not be necessary for SMAs trials because the main outcome is more likely to be based on radiographic improvement.

Sample size calculations and study power

Buckland-Wright published criteria for selecting the study OA knee as follows: (1) the knee must have medial tibio-femoral compartment JSW more than 2 mm; (2) osteophytosis and subchondral sclerosis should be visible; and (3) the joint must have had pain for at least 15 days in one month. The author further suggested that for 2 years' duration, comparing active agent against placebo, the total number of OA knees required to detect a significant difference in minimum JSW using microfocal radiography is 166, 222, and 274 for study power of 80%, 90% and 95%, respectively. The working assumptions are equal patient groups, a mean annual rate of JSN of 0.183 mm/year with a standard deviation of 0.196 mm, a protective effect of 30%, and implementation of computerized measurement of the JSW. The same calculation for standard plain radiographs yielded longer duration and considerably more patients. In another study, Mazzuca et al. estimated that in a 2-year SMA study, 87 patients per group would be necessary to detect a significant difference in JSN between treatment and placebo groups. This group's ‘working assumptions’ were JSN at a rate of 0.25 mm/year, a treatment effect of 30% and a study power of 80%.

These estimates present the number of patients that will ‘complete’ a given SMA trial. It is important to consider the expected high drop out rate in the calculation of the optimal sample size. The accuracy of this type of trial can be further enhanced by radiographic follow-up of all patients even if they dropped out of the study. This will enable the application of the intention-to-treat analysis, in which patients' data are considered in their original group of randomization regardless of compliance. Another important issue to consider is that the adjustment for potential confounding attributes may increase the study power. Therefore, the collection of such data as age, gender, body mass index, physical activity, occupation, and smoking are recommended.

Finally, it is important to emphasize, as discussed earlier, that the actual sample size calculations will be very sensitive to many study-specific parameters, including characteristics of the target study population, sampling technique, imaging method, outcome parameters and expected effect size. This situation might require performing a pilot study before the initiation of any large-scale long-term SMA study and not just relying upon published data.

In conclusion, it is obvious that SMAs have the potential to provide another valuable tool in the armamentarium against OA. However, scientists are faced with several challenges when attempting to document OA progression using available techniques of imaging. Further studies are still required to evaluate and compare the reproducibility and sensitivity of various techniques purported to assess changes in OA disease process.

References


