(type 0) are identified as being of prognostic significance in longitudinal history studies of the disease. Type 0 markers can be used for baseline stratification in clinical trials or as milestones of progression in the natural history of the disease.

Another stage in marker development is assessment of the influence of treatment on the levels of a promising prognostic (type I) marker. A type I biological activity marker is defined as one that responds to therapy. It would likely be evaluated in early stage clinical trials, with the aim of providing proof-of-concept, i.e., that a new treatment indeed has promising activity related to its suggested mode of action. Possibly, a type I biomarker could be used to help estimate the optimal drug dose.

Finally, a type II marker (or composite of several markers) is one that predicts a favorable clinical outcome and thereby reflects the clinical efficacy of a therapeutic intervention. Such a biomarker would be defined as a surrogate marker of therapeutic efficacy. It is likely, however, that any surrogate marker will explain only part of the clinical efficacy, i.e., the proportion of the treatment effect explained (PTE)[4]. As discussed in Reference 3, a correct interpretation of the PTE requires thorough understanding of the underlying mechanisms of the disease and of the activity of the drug. Only if it is known that the agent operates primarily through its action on the marker and the marker is directly in the causal pathway of the disease can changes in marker levels be interpreted reliably.

Validation of a biomarker for its intended use (type 0, I, or II) should follow a stepwise approach, beginning with the initial hypothesis of pathogenesis. Early studies are usually descriptive and cross-sectional cohort studies of limited size. Subsequent validation stages need to expand significantly in size and to be longitudinal, initially retrospective, and later prospective. For biomarkers of type I or type II, access to an active intervention is clearly required.

For a disease-modifying therapy in OA, it may be argued that a clinically meaningful outcome should combine evidence of joint structure (or joint survival) benefit with more direct patient-relevant benefit relating to pain, function, or joint-related quality of life. This clinical outcome would then serve as the gold standard against which any biomarker aspiring to be defined as a surrogate OA marker (type II) needs to be validated. It would appear important that investigators in the field agree on a standard clinical endpoint for each proposed use of a biomarker or surrogate marker. If a "molecular" biomarker is validated against only a "structural" joint outcome, it may serve to examine the relationship of one biomarker to another, but not against a clinical outcome.

This does not necessarily mean that a biomarker that is not fully validated as a surrogate outcome is not useful. It may indeed be useful, insofar as it may help identify a treatment target, or monitor *in vivo* or *in vitro* specific cellular or molecular process of interest in drug development. Biomarker validation is not an all-or-nothing issue, but a process of gradual strengthening of evidence. In validating a biomarker, studies will likely need to account for interactions generated by the particular joint studied (e.g., knee vs hip), stage of disease, comorbidities and medications, ethnicity, sex, age, body mass, and other factors.

The absence of a drug or treatment with unambiguous disease-modifying activity in OA (however defined) greatly hampers any attempt to validate a type II biomarker for OA. Current biomarker work in OA is therefore largely limited to the search for type 0 and type I biomarkers. Most OA-related work to date has taken the "candidate protein" approach of exploring changes in body fluids (blood, urine, synovial fluid) of concentrations of a protein (or fragment thereof) with a known or suspected function in joint cartilage. While several promising candidate markers have been identified through this process[5], this approach has its limitations.

It may be argued that the search for OA biomarkers needs to be expanded genome-, proteome-, and metabolome-wide and accelerated through greater use of large-scale techniques, such as those used in proteomics and exploration of changes in gene expression in joint tissues and circulating blood cells. Finally, for the advancement of biomarker research using either traditional or newer approaches, access to large repositories of biological specimens that are linked to high quality longitudinal clinical data is critical. Given the slow progression of OA, this may be the limitation that is most difficult to overcome.

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ADVANCES IN RADIOGRAPHIC IMAGING OF PROGRESSION OF HIP AND KNEE OSTEOARTHRITIS

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Measurement of joint space width (JSW) remains the recommended method for the evaluation of therapies intended to prevent or retard the progression of OA[1]. However, it has become apparent that the evaluation of hip or knee joint

space narrowing (JSN) in serial radiographs is difficult[2]. The main issues underlying accurate evaluation of JSN include sensitivity of the method of measurement, acquisition of high quality, clinically relevant joint images, and reacquisition of the same joint image in serial radiographs. Considerable effort has been made over the past 2 years to help improve each of these.

Measurement of JSW

JSW can be measured manually or with computer software; however, the best method is not clear. Both approaches permit measurement of the minimum JSW (mJSW, i.e., the interbone distance at the narrowest point of the tibiofemoral compartment), but only the computer method permits measurement of the mean JSW within an area of interest. Several new manual and computerized methods have recently been proposed[3-8]. It has been suggested that mean JSW is more reproducible[6] and more sensitive to change[5] than mJSW, but the latter remains the more generally recommended and accepted outcome measurement[2].

Recent comparisons of manual and automated methods for the measurement of mJSW have yielded no new information. In a study of hip joint OA[3] the 2 methods appeared to have equivalent reliability and sensitivity, but in a knee OA study employing the standard extended anteroposterior (AP) view, automated measurement was found to be superior to the manual method[5]. In contrast, for measurement of JSW in semiflexed AP radiographs of the OA knee[9], the manual method was found to be superior to the automated method because it provided greater accuracy in correcting for the radiographic magnification inherent in the semiflexed AP view of the knee. Obviously, the reliability of measurement can vary with the degree of expertise of the observer. It probably also varies among different automated methods. Head-to-head comparisons of manual measurements made by experienced observers and by computer are lacking.

More recent reports of methods of measurement of JSN claim higher levels of reliability than older methods. Nevertheless, even with the most reproducible methods, the smallest standard deviation of the difference between test and retest measurements barely reaches 0.1 mm, indicating a smallest detectable difference (SDD) of at least 0.2 mm. Considering that the average annual rate of JSN in OA joints is only 0.10–0.15 mm, that SDD is relatively large.

Reproducible Acquisition of Joint Images

The hip joint. Acquisition of a hip joint image generally relies on an AP pelvis radiograph, preferably obtained in weight-bearing[2]. The reproducibility of the image of the hip joint in serial radiographs of the pelvis is considered to be acceptable and an AP view of the pelvis, rather than unilateral radiographs of the hip joints, remains the recommended view[1]. However, comparative studies of the AP view of the pelvis and the hip profile of Lequesne indicated that the site of mJSW was poorly imaged in the pelvis radiograph in about 30% of patients, especially if migration of the femoral head was not superolateral[2]. Longitudinal studies using the Lequesne hip profile are in progress, but the reproducibility of the images in serial hip profile radiographs is currently unknown.

Newer studies of hip OA have not been published recently, but further evaluations of the ECHODIAH study (a placebo controlled trial of the anthraquinone derivative, diacerein) have now been completed and suggest that a change in JSW ≥ 0.4 mm over 3 years is relevant to the patient[10], based upon a predicted requirement for total hip replacement. In another study, the same investigators suggested that 0.2 mm of JSN over 1 year and 0.4 mm over 2 years were relevant, based on expert opinion of whether clinically relevant deterioration had occurred[11]. This emphasizes the marginal sensitivity of radiographic measurement of the hip joint and the need for clinical trials of at least 3 years' duration in patients with typical hip OA.

It is important to understand the limitations in analyses of the results of clinical trials that compare the number of progressors in each treatment group (rather than, e.g., the mean rate of JSW). Although the SDD is the logical cutoff value with which to define progressors (i.e., to identify patients in whom true JSN has occurred), analysis of progressors is relevant only when the cutoff value for SDD is smaller than the expected mean value for JSN in the study. For example, in the ECHODIAH study, analysis of progressors was legitimized by the fact that mean JSN (and the level of JSN in a majority of patients) over the 3-year period of the trial was greater than the 0.5 mm cutoff value for SDD. However, an analysis of progressors in a study with an SDD cutoff value of 0.5 mm and an expected mean value for JSN of only 0.2–0.3 mm could be misleading insofar as it would select only patients with an abnormally high rate of JSN.

The knee joint. The standing AP radiograph of the knee in extension is now recognized as a poor radiographic view for measurement of femorotibial JSW and detection of changes in JSN in serial films. The superiority of knee radiographs in flexion rather than in extension for detection of JSN at the most common site of maximum cartilage loss has been confirmed.

Importantly, standing extended AP view has low sensitivity for identification of early femorotibial OA; among subjects who exhibited unilateral knee OA in a conventional standing extended AP radiograph, when the apparently normal contralateral knee was imaged in flexion, femorotibial OA was apparent in 52% of cases[12]. Similarly, we have demonstrated the superiority of radiography of the knee in flexion, in comparison with the standing AP view, for demonstrating medial or lateral tibiofemoral JSN in early OA.

Four standardized radiograph protocols have been developed and characterized: the semiflexed AP view, semiflexed

PA metatarsophalangeal (MTP) view, fixed-flexion PA view, and the PA Lyon schuss view. Among these, 2 (the semiflexed AP and Lyon schuss) require fluoroscopy to position the knee. Only the semiflexed view employs an AP orientation of the x-ray beam. Although the latter protocol has been shown to represent a significant improvement over the standing extended AP view, its performance is affected by the need to correct for radiographic magnification. In contrast, the PA views of the knee in flexion do not require magnification correction and appear simpler and preferable to an AP view.

The position of the knee is identical in the Lyon schuss and fixed-flexion views. The major differences between these 2 radiographic protocols are in the use of fluoroscopy to adjust the angle of the x-ray beam to achieve optimal alignment of the medial tibial plateau in the former and the use of a Plexiglas frame to standardize knee flexion and foot positioning in the latter.

In the semiflexed MTP protocol, which does not use a positioning frame or fluoroscopy, knee flexion is less than in the fixed-flexion or Lyon schuss view by the length of the big toe. A head-to-head comparison of the 3 flexed PA views is currently lacking. However, reproducible alignment of the medial tibial plateau with the x-ray beam, as assessed by the intermargin distance (IMD) of the medial tibial plateau, is a major factor in the reliable measurement of changes in JSW in serial radiography and improves sensitivity to change[13]. In the Lyon schuss view, the optimal alignment of the medial tibial plateau that provides the greatest sensitivity to change in JSN requires an IMD < 1.2 mm[14]. While high performance of both the MTP and the fixed-flexion views has been reported, the reproducibility of alignment in serial MTP radiographs has been questioned[15]. In patients positioned with the Lyon schuss protocol, the quality of alignment is highly dependent upon use of fluoroscopy[16]. Reproducibility of the angle of knee flexion has been shown to be superior in the fixed flexion view to that in either the MTP view or semiflexed AP view. Thus, the data support the use of fluoroscopy for optimal alignment of the medial tibial plateau and of a Plexiglas frame to improve standardization of the angle of knee flexion.

Conclusion

Due to the great difficulty in obtaining high quality reproducible images of OA hips and knees, when the low average annual rate of JSN in the OA joint is taken into account the accuracy of JSW measurement in serial radiographs remains only marginal. For this reason, the duration of clinical trials of structure-modifying OA drugs remains lengthy. Further improvements in the acquisition of serial, high quality joint images should continue to improve the radiographic assessment of progression of hip and knee OA.

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UPDATE ON CARTILAGE OLIGOMERIC MATRIX PROTEIN AS A MARKER OF OSTEOARTHRITIS

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Cartilage oligomeric matrix protein (COMP), a 524 kDa