

New Strategies for Clinical Trials of OA: Evidence from a Longitudinal Trial of Radiography, MRI Morphometry and Molecular MRI

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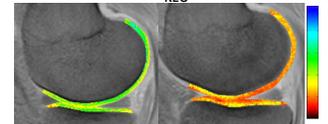
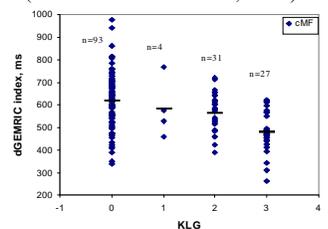
INTRODUCTION: Despite years of study and numerous clinical trials, osteoarthritis (OA) remains poorly understood, and a disease modifying OA drug (DMOAD) has not yet been approved for clinical use. This motivates a need for new set of strategies for carrying out clinical studies of OA. In the current report, analysis of data from a 2 year multicenter trial of radiography, MRI morphometry, and dGEMRIC are presented and utilized to delineate potential new strategies for future trials of OA.

METHODS: A total of (n = 155) of the Pfizer A9001140 observational MRI study data was evaluated; n=93 with no radiographic OA (KLG 0), n=4 KLG1, n=31 KLG 2 and n=27 KLG 3. MRI was acquired at 7 clinical sites. Morphologic data (Eckstein, Ann. Rheum Dis 2008) and dGEMRIC (Williams MRM 58:830, 2007) were obtained and analyzed as previously described. These data were utilized for the analyses described below.

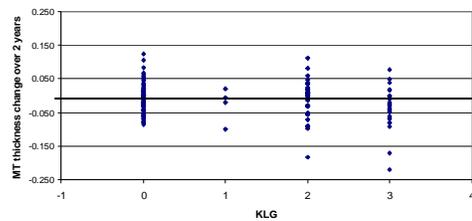
RESULTS / DISCUSSION:

Strategy A: Kellgren-Lawrence Grading (KLG) alone may not be optimal to define cohorts. Three sets of data motivate the use of a strategy other than KLG alone for defining cohorts:

(i) **KLG0 may not be a “healthy control” cohort.** As seen in the Figure, dGEMRIC values in the central medial femur (cMF) as a function of KL Grade, there are a large number of individuals with low dGEMRIC values in the putative “control” group (KL0), comparable to the low values seen in the cohort with significant disease (KL3). In the example of the dGEMRIC images from the medial compartment of two KL0 knees, although both are considered “controls” and appear to have full-thickness cartilage, large differences in the molecular metrics of disease are apparent.



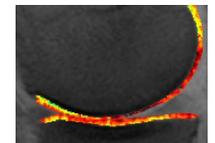
Data interpretation may therefore be compromised by referencing the data from the disease cohort to a mixed group. Future trials might be improved by not considering KL0 as a single cohort. Alternatively, grouping of subjects in clinical trials potentially may be based on combined biochemical and morphologic metrics.



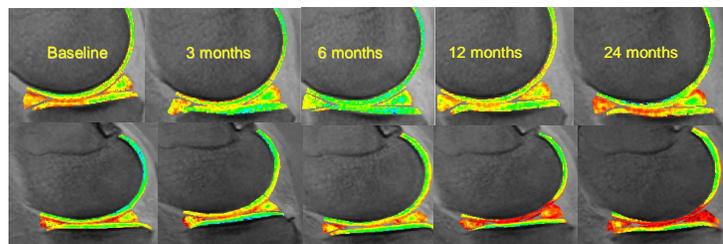
(ii) **Fast “progressors” are seen in all KL grade cohorts.** The change in cartilage thickness over a two year period, a metric typically used to define “progression”, is shown in the Figure to the left for the medial tibia. Statistically, only KL3 knees “progress”, i.e. lose cartilage thickness, motivating the use of KL3 for clinical trials. The reality is that many of the KL0 knees also lost thickness at a comparable level as most of the KL3 knees; however others gained in thickness, so that as a group the average change wasn’t significantly different than zero.

If cartilage thickness change is to be used as a metric of progression, grouping by KL grade does not delineate cohorts which separate out those who progress from those who do not.

(iii) **Progression within KL3 is seen in knees with little cartilage.** The image to the right is an example of a KL3 knee which showed high progression, ie loss of cartilage thickness over two years.



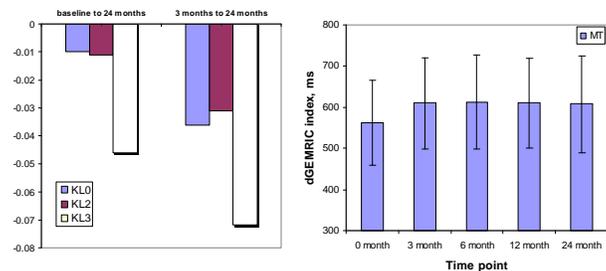
By forcing cohort delineation by KL grade, and hence focusing on the progressors in KL3 with relatively little tissue remaining, many of the knees studied in trials may not be able to respond to the intervention.



Strategy B: Focus on “vulnerable cartilage” and reversibility of disease.

Focal lesions in tissue molecular status progress and recede over time. The images (top) show dGEMRIC lesions in the anterior meniscus and tibial plateau at baseline, less at 3 and 6 months, and then reappearing at 12 months and worsening at 24 months. The ratio of tibial lesion to surrounding tissue is 0.70, 0.86, 0.90, 0.80, 0.63 at baseline, 3, 6, 12, and 24 months. Such reversible lesions are seen in a number of cases and a number of areas (tibia and femur, medial and lateral). In other cases (e.g. bottom), the focal lesion progresses over time (in both cartilage and meniscus). Still in others (not shown), the lesion is constant.

Long term tracking of these lesions and/or correlation with other metrics of joint health is necessary to determine which of these lesions may go on to cartilage loss and therefore when intervention might prevent such loss. This information might provide a better cohort for potential impact of preventative measures and/or interventions. In addition, the data highlight the ability for the joint tissues to adapt, motivating strategies for evaluating intervention to reverse degeneration even before trying to halt “progression” of disease, thus potentially eliminating some of the difficulties with the progression metrics described above.



Strategy C: A physiologic effect of entry to a clinical trial may need to be taken into account. (a) Cartilage thickness loss of the MT cartilage between enrollment (baseline) and month 24 is less than cartilage thickness loss defined between month 3 and month 24, indicating that there might have been an effect on thickness between enrollment and month 3 of the trial. (b) dGEMRIC of the MT over time. There is an increase of approximately 8% of the Index at the 3 month timepoint, which was then relatively stable over the next 2 years.

Sensitivity to effects in prior studies may have been reduced if entry data were used as “baseline”; future studies may do better with a period of equilibration before baseline scans are taken.

One of the issues potentially preventing MRI from having a larger impact in OA is that the strategies utilized for clinical trials are those based on radiographic paradigms. The current report, by evaluating data from a longitudinal trial of radiography and morphologic and molecular MRI, represents one step in the process of redefining these strategies such that future clinical trials might be more successful. Studies with other molecular metrics of cartilage and MRI metrics of other tissues of the joint should extend these results and lead the way for an improved characterization and understanding of joint degradation and repair.