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Review

Imaging of cartilage and bone: promises and pitfalls in clinical trials of osteoarthritis

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SUMMARY

Imaging in clinical trials is used to evaluate subject eligibility, and/or efficacy of intervention, supporting decision making in drug development by ascertaining treatment effects on joint structure. This review focusses on imaging of bone and cartilage in clinical trials of (knee) osteoarthritis. We narratively review the full-text literature on imaging of bone and cartilage, adding primary experience in the implementation of imaging methods in clinical trials. Aims and constraints of applying imaging in clinical trials are outlined. The specific uses of semi-quantitative and quantitative imaging biomarkers of bone and cartilage in osteoarthritis trials are summarized, focusing on radiography and magnetic resonance imaging (MRI). Studies having compared both imaging methodologies directly and those having established a relationship between imaging biomarkers and clinical outcomes are highlighted. To make this review of practical use, recommendations are provided as to which imaging protocols are ideal for capturing specific aspects of bone and cartilage tissue, and pitfalls in their usage are highlighted. Further, the longitudinal sensitivity to change, of different imaging methods is reported for various patient strata. From these power calculations can be accomplished, provided the strength of the treatment effect is known. In conclusion, current imaging methodologies provide powerful tools for scoring and measuring morphological and compositional aspects of most articular tissues, capturing longitudinal change with reasonable to excellent sensitivity. When employed properly, imaging has tremendous potential for ascertaining treatment effects on various joint structures, potentially over shorter time scales than required for demonstrating effects on clinical outcomes.

Introduction

Clinical trials are designed to objectively test the effect of an intervention on the disease process. In osteoarthritis (OA), clinical outcomes (pain and function) are unable to elucidate whether the effect of intervention is purely symptomatic or modifying the disease process at a structural, joint tissue level. While molecular markers from serum or urine may identify processes of tissue formation and degradation, they represent all body tissue turn-over. Evaluating interventions at specific joints and tissues thus has to rely on imaging.

Imaging measures should be accurate, precise (reliable), specific, sensitive to longitudinal change, and acceptable to regulatory agencies. Current regulatory guidance for approval of disease modifying OA drugs (DMOADs) recommends that reduction of structural pathology in joint tissue should be accompanied by benefits in clinical outcomes. Studies relating imaging "biomarkers" to clinical outcomes therefore are of particular interest. All synovial joint tissues are known contribute to the development or progression of OA. However, articular cartilage warrants almost

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frictionless transmission of dynamic forces in joints, and when cartilage is lost and subchondral bone exposed, joint function declines. This review therefore focuses on imaging of cartilage and bone tissue in clinical trials.

The authors searched literature from Pubmed up to January 1st, 2014. Studies were prioritized for inclusion, when critically evaluating reliability, sensitivity to change, association with clinical outcomes, and efficacy in evaluating treatment effects for certain imaging methods, or when comparing different methodologies directly. Primary experience in implementing imaging methods was added, with the authors having a variety of backgrounds, including radiology, anatomy, rheumatology, medical image data analysis, work in a clinical research organization, or in the pharmaceutical industry. Recommendations are provided as to which imaging protocols are ideal for capturing specific aspects and imaging metrics of specific tissues (Table I), and pitfalls in their usage are outlined. Where available, sensitivity to change will be reported as "standardized response mean" (SRM) (Table II). Given the heterogeneity of study populations and observation periods, no attempt was made to derive summary measures across studies, or measures of consistency and risk bias. Rather, results were tabulated covering a wide range of conditions, to provide estimates of sensitivity to change for a variety of selection criteria and design parameters (Table II).

Primary aims and constraints of clinical trials

Medical imaging is used for screening, diagnosis/prognosis, evaluating the natural history of disease, or monitoring therapy. Imaging requirements for safety evaluations will not be considered here, given space limitations. In efficacy evaluation, imaging is used for monitoring natural history (placebo) vs therapy. The metrics to be satisfied by imaging parameters for clinical trials have been described[1]. A key metric is "precision" (also "reproducibility" or "reliability"), which refers to the degree to which repeated (test–retest) measurements show the same result under unchanged conditions. Currently only radiographs are accepted for DMOAD Phase III trials by regulatory agencies, but there is new guidance that may provide a pathway for the utilization of magnetic resonance imaging (MRI) (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf), whereas in cartilage repair MRI already has been accepted as an endpoint.

The decision of which imaging technique to use in a clinical trial depends on the mechanism of DMOAD action. Radiographic assessment of femorotibial "joint space width (JSW) or narrowing" (JSN) represents a composite measure, because more than one tissue is present between femoral and tibial subchondral bone. MRI is more specific to a variety of articular tissues, but careful consideration must be made as to which joint region and tissue is to be evaluated, and which specific scoring or measuring methods are to be applied. For MRI of the knee, magnets with $\geq$1.5 T and dedicated knee coils are highly preferable. Subtle differences have been reported between quadrature and phased array coils[2,3], the latter providing greater signal. Signal homogeneity, high contrast-to-noise, minimization of technical artifacts, and full anatomical coverage of structures of interest are crucial. Patient positioning, image orientation, and spatial resolution must be matched to the specific goals and measurement method. Compromises have to be achieved regarding acquisition time, patient comfort, cost, image quality, resolution, and number/types of imaging protocols obtained supporting various imaging measures (Table I). Monthly phantom measurements and quality assurance procedures in the Osteoarthritis Initiative (OAI) have revealed that geometric MRI measures were consistent between different sites, and that geometric measures and MRI relaxation times (T2) were stable over now up to 8 years follow-up[4]. Whichever imaging and scoring/measurement method used, central review of the images by expert readers is highly preferable[5]. These have to agree on the specific approach before evaluating images, to ensure consistent application of scoring or measurement technology. Further, intra- (and inter-) reader variability should be tested within clinical trials, to ensure consistency and precision under specific conditions. In cross-sectional studies, the inter-observer error must be substantially lower than the between-subject variability to ensure robust differentiation of study participants. In longitudinal studies, baseline and follow-images should always be evaluated by the same reader, because intra-observer errors are generally smaller than inter-observer errors[6]. Preferably, also, the intra-observer error should be small in relation to the "effect" that is being measured to avoid large sample sizes[7].

Use of radiography in OA clinical trials

Radiographic acquisition techniques and quality control

Radiographs can be used for establishing disease severity during screening to determine patient eligibility, and for evaluating disease progression with and without DMOAD treatment. While historically diagnosis and disease severity have been established on

Table I
MRI acquisition techniques supporting different imaging measures used in clinical trials

Imaging measure	Image acquisition required	Recommended resol.		Key validation papers	Other recommendations
		SlTh	In plane		
Cartilage lesion scoring	IW F/TSE	3 mm	≤0.5 mm	Refs. 56,57	2–3 planes and TE < 45 ms required
BML scoring	IW F/TSE fs	3 mm	≤0.5 mm	Refs. 58,59	2–3 planes and fs required
Cartilage thickness/volume	FLASH/SPGR/FFE/WATSc fs/we	≤1.5 mm	≤0.35 mm	Refs. 60–62	TE < 10 ms
	DESS we	≤1.5 mm	≤0.35 mm	Refs. 65,66	With 0.7 mm every second slice sufficient
Cartilage composition					
T2	MESE (6–7 echos)	3 mm	≤0.7 mm	Refs. 2,117,120	Eliminate shortest (10 ms) TE from fit
T2/diffusion	DESS	1.5 mm	≤0.35 mm	Refs. 118,119	Potentially simultaneous thickness analysis
T1rho	500 Hz spin lock	3 mm	≤0.7 mm	Refs. 120,122,123	Spin lock followed by SE or GRE readout
dGEMRIC	T1-mapping	3 mm	≤0.7 mm	Refs. 116,124,125	Requires iv Gd injection 90 min before
Sodium	PR or cones	4 mm	≤1.2 mm	Ref. 128	Requires specialized coil and high field
CEST	Multiple RF pulses	3 mm	≤0.7 mm	Refs. 129,130	Requires high field (3 or 7 T)
Ultra-short TE	PR or cones	3 mm	≤0.7 mm	Ref. 131	TE < 5 ms (available in 2D or 3D)

IW F/TSE fs = intermediate weighted fast or turbo spin echo sequence with fat suppression, SE = spin echo, GRE = gradient echo, T2 = measurement of the spin–spin relaxation time, T1rho = measurement of the spin-lattice relaxation time, iv = intravenous, Gd = gadolinium, SlTh = slice thickness, resol. = resolution, PR = projection-reconstruction.