Imaging Biomarkers: MRI vs. X-Ray

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Imaging Biomarkers in OA
MRI vs. X-ray

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OARSI Clinical Trial Recommendations


Review

OARSI Clinical Trials Recommendations: Knee imaging in clinical trials in osteoarthritis

“Summary and Conclusion:
The goals of imaging the knee in clinical trials can include subject selection, monitoring disease progression and treatment effect, and/or identifying complications of the disease or the treatment."

AKA:

• Eligibility
• Outcome Measure /Surrogate Endpoint
• Safety Monitoring
Eligibility
Eligibility: Kellgren-Lawrence - Ordinal Grading

„early to moderate disease“

KL 0  KL 1  KL 2  KL 3  KL 4
No ROA  ROA
BUT! KL2 and 3 knees are very heterogeneous!

- e.g. in MOST Study 21% of KL2 knees have no cartilage damage in the MTFJ (and 41% in the LTFJ)!
- 25% of KL2 show severe wide-spread full-thickness damage medially

=> KL2 (and 3) is not a homogeneous sample of “early-to-moderate” OA!
Eligibility: Exclude adverse findings at BL affecting efficacy!

Baseline **SIF** medial femur only seen on MRI! Other findings: e.g. bone marrow infiltration, meniscal root tears, occult fractures etc. NOT modifiable by any DMOAD!
“Regarding enrichment, there is considerable interest in identifying the subset of the patient population for whom an intervention would have a clinically meaningfully favorable benefit-to-risk profile due to greater benefits or fewer adverse outcomes."
Enrichment:
OA is not one disease!

• Enrichment by MRI for superior structural disease characterization considering **mode of action** of product

• Enrichment for certain structural **MRI-defined phenotypes**: Inflammation, Bone, Cartilage, Atrophic etc.

• Enrichment for “**Subjects-at-Risk**” defined by structure and symptoms
**Enrichment by MRI:**
**Superior structural disease characterization**

**Anabolic** compound: Cartilage damage => Cartilage can grow!
An **anabolic** compound can only work if there is cartilage loss => exclude knees without cartilage loss

=> 30 % of KL2 knees in OAI/FNIH study had no medial TF cartilage damage!
An **anticatabolic** compound can only work if there is something to preserve! = consider excluding wide spread full thickness cartilage loss!
Enrichment for structural MRI-defined phenotypes

Target inflammation => Inflammation should be present!

Selection for low mJSW and moderate-to-high pain at baseline (i.e. "Subjects-at-Risk") demonstrated translation of structure modification into symptomatic benefit.
Structural Endpoint/Surrogate Outcome
X-ray highly dependent on standardized image acquisition!

JSN is non-specific
(cartilage, meniscus damage, meniscal extrusion)
Non-Sensitive

(slow; only central joint visualized)
Tissues involved in the OA process

Cartilage
Meniscus
Subchondral cyst
PCL/ACL
MCL/LCL
Bone marrow lesion
Capsule
Effusion
Periarticular cyst
Synovitis
Muscle
Different imaging approaches to OA joint assessment using MRI available:

- **Quantitative Analysis**
  - (cartilage, meniscus, muscle)

- **Semiquantitative Analysis**
  - (all joint tissues, eligibility)

- **DCE MRI**
  - (synovitis/inflammation)

- **Compositional Analysis**
  - (cartilage, meniscus, muscle)

- **Bone Shape**

- **Metabolic Imaging (PET-CT/MRI)**

Possible Outcome Measures depending on target tissue:

- **Cartilage**: q MRI, SQ MRI, compositional MRI (early disease, tissue quality)

- **Inflammation**: DCE MRI, non-enhanced SQ MRI (Hoffa- effusion-synovitis, contrast-enhanced SQ MRI (11 point scoring), effusion volume assessment, possibly metabolic imaging like PET MRI/CT

- **Subchondral Bone**: SQ MRI, volume assessment, perfusion parameters (DCE MRI), bone structure, bone shape
Safety
Safety

Many structural safety findings are not visualized by X-ray!

Tumor (GCTTS)  Osteonecrosis  Systemic disease (leukemia)
Summary: X-ray vs. MRI

X-ray: Needed for baseline disease characterization (severity)

X-ray: Non-sensitive to change and non-specific

X-ray: Challenging to acquire in reproducible fashion in clinical trials

X-ray: Does not show findings that may be affecting efficacy (at BL) or considered safety concerns (on-trial)

MRI: Ready for Screening Purposes/ Eligibility

MRI: Eligibility - Helps in Enrichment

MRI: Endpoint - MRI-Methods are complementary; choice depending on mode of action, target tissue and length of trial