A simple inclusion criteria combination increases the rate of cartilage loss in patients with knee osteoarthritis

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ABSTRACT

Objectives: Selection of patients with KL radiographic grade 2 and 3 is widely used in clinical trials, but this approach could have some limitations. The purpose of this study performed on OsteoArthritis Initiative (OAI) data is to assess whether adding OARSI-JSN to KL grading could select a population with increased rate of cartilage loss. Indeed, KL is not compartment-specific and not uniformly graded amongst expert readers. OARSI-JSN is another established, compartment-specific grading scale that specifically captures the joint space narrowing from radiographs.

Design: 1019 knee radiographs data from the progression cohort of the OAI public database were used. Cartilage loss measured with magnetic resonance imaging was evaluated using change over 1 year from baseline in cartilage thickness in the central Medial Tibio-Femoral Compartment (cMTFC) in the KL2-3 and KL2-3+JSN1-2 populations.

Results: The mean cMTFC cartilage loss over one year was \(-0.135 \pm 0.29\) mm (median \(-0.095\) mm) in the KL2-3 population and \(-0.176 \pm 0.29\) mm (median \(-0.140\) mm) in the KL2-3+JSN1-2 population.

Conclusions: OARSI-JSN appears to be an effective inclusion criterion to be considered in combination with the KL grade in future clinical trials testing the structural efficacy of DMOADs in a time window of 1-year as it contributes to identify knees in whom the disease progresses rapidly.

1. Introduction

Knee Osteoarthritis (OA) is a common chronic disease with slow progression and no approved disease-modifying drugs (DMOADs). To date, no clear criteria have been established to discriminate patients in whom the disease may progress rapidly and may benefit most from treatment. This situation hampers the development of DMOADs [1]. The first and most widely radiographic grading scale used was proposed by Kellgren and Lawrence (KL), and it has been recommended to include patients with KL grades 2 or 3 in clinical trials evaluating DMOADs [2]. However KL grades are neither compartment-specific, nor uniformly graded amongst expert readers, given the complexity of multiple features being combined to a 0–4 scale. OARSI-JSN is another established grading scale [3] that specifically captures the compartment-specific radiographic joint space narrowing [4]. The purpose of this study was to assess in a large OA cohort (OAI) to what extent adding Osteoarthritis Research Society International joint space narrowing (OARSI-JSN) to KL grading could select a population with increased rate of cartilage loss.

2. Method

Data of cartilage loss measured using quantitative magnetic
resonance imaging (MRI) with corresponding knee radiographs (n = 1019) were obtained from the progression cohort of the OsteoArthritis Initiative (OAI) public database [5]. Cartilage loss was evaluated using change over 1 year from baseline in cartilage thickness in the central Medial Tibio-Femoral Compartment (cMTFC), the cartilage subregion where the loss was observed to be the most responsive to change [6] and which was also shown to be associated with progression as part of the OAI FNIH project [7] and with subsequent knee replacement surgery [8]. The cartilage readings were performed by a group of experienced readers, who were blinded to timepoint. All segmentations were done manually and were quality-controlled by an expert reader.

Two analysis populations were compared on the target knee (see supplementary data for target knee definition): the KL2,3 population commonly selected for trials evaluating DMOADs [9], and a “KL2,3+JSN1,2” population, to which we added medial OARSI-JSN grade 1 or 2 as inclusion criterion. Comparison between both populations has been done with descriptive statistics (median, mean, standard deviation, standardised response mean, 95% confidence intervals). P-values from Student t-test, testing null hypothesis μ = 0 (μ = population mean change over 1 year) are also given. All analyses have been performed with R software.

Both KL and OARSI-JSN were taken from version 0.8 of the central radiographic readings performed at Boston University by two radiologists. In case of disagreement, between them, a consensus reading took place. Patients or the public were not involved in this research.

3. Results

Baseline characteristics for both KL2,3 and KL2,3+JSN1,2 populations are summarised in Supplementary Table. Grade of severity at baseline and cartilage loss are given in Table 1 for both populations.

The mean cMTFC cartilage loss over one year was −0.135 ± 0.29 mm (median = −0.095 mm) in the KL2,3 population and −0.176 ± 0.29 mm (median = −0.140 mm) in the KL2,3+JSN1,2 population.

In the KL2,3 population, knees with a JSN grade 0 scoring did not show any cartilage loss (−0.048 ± 0.24 mm). The mean cartilage loss in KL2 knees, of whom 47% were medial OARSI-JSN grade 0, was −0.077 ± 0.26 mm (median = −0.048 mm). The mean cartilage loss was −0.180 ± 0.30 mm (median = −0.140 mm) in KL3 knees, of whom 22% were medial OARSI-JSN grade 0. One should note that all these KL3 knees had lateral OARSI-JSN grade 2.

In KL2,3+JSN1,2 population, the mean cartilage loss was −0.089 ± 0.24 mm (median = −0.060 mm) in KL2 knees and −0.224 ± 0.31 mm (median = −0.178 mm) in KL3 knees.

All intra group p-values are lower than 0.01 meaning that there is a statistically significant cartilage loss in all sub-populations presented.

It can be noted that SRM presented in Table 1 are greater for KL3 and medial OARSI-JSN2 knees (between 0.60 and 0.74) than for KL2 and medial OARSI-JSN1 knees (between 0.30 and 0.37), meaning the magnitude of cartilage change is more important for KL3 and medial OARSI-JSN2 knees.

Sensitivity analyses were performed according to definition of the femoral region. Results were very consistent (see supplementary data).

4. Conclusion

To conclude, the OARSI-JSN appears as an effective inclusion criterion to be considered in combination with the KL grade in future clinical trials testing the structural efficacy of DMOADs in a time window of 1-year. It contributes to the identification of knees in which cartilage loss progresses more rapidly. It is important to point out that KL and JSN grading were very well controlled in OAI, therefore central grading by a few experienced readers would be necessary in clinical trials in order to keep a low level of inter and intra-observer variability. Our analysis based on a clinical hypothesis can provide some key elements to support the design for future OA trials.

Author contributions

Olivier Imbert, Damien Chimits, Mickaël Guedj and Freddy Lorieau contributed to study design, data cleaning and data analysis. All authors contributed to data interpretation, writing of the report, revising it critically and approved the final version to be published and agree to be accountable for all aspects.

Table 1

| Grade of severity at baseline | KL2,3 population (N = 599) | KL2,3+JSN1,2 population (N = 419) |
|-----------------------------|---------------------------|---------------------------------|
|                             | N (%)                     | N (%)                           |
| KL2                         |                           |                                |
| With medial OARSI-JSN 0     | 258 (43.1)                | 151 (36.0)                      |
| With medial OARSI-JSN 1     | 122 (47.3)                | NA                              |
| With medial OARSI-JSN 2     | 136 (52.7)                | 151 (100)                       |
| KL3                         | 0 (0.0)                   | 0 (0)                           |
| With medial OARSI-JSN 0     | 341 (56.9)                | 268 (64.0)                      |
| With medial OARSI-JSN 1     | 75 (22.0)                 | NA                              |
| With medial OARSI-JSN 2     | 3 (0.9)                   | 3 (1.1)                         |
| cMTFC cartilage loss over one year |                   | 265 (71.1)                      |
| All knees                   | 599 (100)                 | 265 (98.9)                      |
| With medial OARSI-JSN 0     | −0.095 (−0.135, 0.29)     | 419 (−0.140)                    |
| With medial OARSI-JSN 1     | −0.046 (−0.112, 0.001)    | −0.089 (−0.176, 0.029)          |
| With medial OARSI-JSN 2     | −0.077 (−0.267, 0.045)    | −0.089 (−0.248, 0.001)          |
| KL3                         | −0.176 (−0.29, 0.001)     | −0.089 (−0.248, 0.001)          |
| With medial OARSI-JSN 0     | −0.180 (−0.30, 0.001)     | −0.224 (−0.31, 0.001)           |
| With medial OARSI-JSN 1     | −0.200 (−0.34, 0.001)     | −0.224 (−0.31, 0.001)           |
| With medial OARSI-JSN 2     | −0.227 (−0.31, 0.001)     | −0.228 (−0.31, 0.001)           |

a SRM (Standardised Response Mean) = mean.sd.
b 95% confidence interval of the mean.
c P-value from Student t-test (null hypothesis: Mean = 0).
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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2021.100188.

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