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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Other

Conflict of Interest

http://yoda.yale.edu/system/files/yoda_project_coi_dvdh_26_01_2018.pdf

http://yoda.yale.edu/system/files/yoda_project_coi_fvg_26_01_2018.pdf

http://yoda.yale.edu/system/files/yoda_project_coi_mlm_26_01_2018.pdf

http://yoda.yale.edu/system/files/coi_yoda_sofia_ramiro_february_2018.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA

Project Data Use Agreement Training

Associated Trial(s):

1. [NCT00207701 - A Randomized, Double-blind Trial of the Efficacy of REMICADE \(Infliximab\) Compared With Placebo in Subjects With Ankylosing Spondylitis Receiving Standard Anti-inflammatory Drug Therapy](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Relationship between decreased bone mineral density and syndesmophyte development: a multilevel analysis in patients with Ankylosing Spondylitis

Narrative Summary:

The purpose of this study is to investigate in ankylosing spondylitis (AS) patients the relationship between decreased vertebral bone mineral density (BMD) by Dual-energy x-ray absorptiometry (DEXA) and the radiographic formation of syndesmophytes at the vertebral level, after 2 years. In addition we aim to explore the possible association between baseline MRI vertebral corner inflammation and fat deposition on the one hand and decreased BMD on the other hand. Multilevel analysis will adjust for the within patient correlation across multiple vertebrae and reader, taking potential confounders into account. Addressing these issues will give us more insight into syndesmophyte formation.

Scientific Abstract:

Background: To our knowledge, neither a relationship between bone loss and MRI inflammation/fat deposition at the same site nor the relationship between the presence of low bone mineral density (BMD) and the development of syndesmophytes, at a vertebral unit level, has ever been analysed in patients with ankylosing spondylitis (AS).

Objective: The purpose of this study is to investigate the relationship between decreased baseline BMD and the development of syndesmophytes after 2 years. In addition, we aim to explore the possible association between baseline MRI vertebral corner inflammation (VCI) and vertebral corner fat deposition (VCFD), on the one hand, and decreased BMD, on the other hand.

Study Design: Post-hoc analysis from a randomized controlled trial.

Participants: Patients with AS who have a baseline BMD at the lumbar level, as well as spinal radiographs (baseline and 2 years) and a spinal MRI (baseline).

Main Outcome Measures: Of the first analysis, the main outcome is new syndesmophyte formation, as assessed by the individual vertebral corner scores of the modified Stoke AS spine score (mSASSS), changing from a score <2 at baseline to a score ≥2 at 2 years of follow-up. Of the second analysis, the main outcome is the presence of decreased baseline BMD at a vertebral level (L1 to L5) assessed by Dual-energy x-ray absorptiometry.

Statistical Analysis: Data will be analyzed at the vertebral unit level using a multilevel analysis approach to adjust for within-patient correlation across multiple vertebrae and reader, taking potential confounders into account.

Brief Project Background and Statement of Project Significance:

Ankylosing spondylitis (AS) is a chronic inflammatory disease characterized by reversible inflammation and irreversible structural damage of the spine [1]. Structural damage in AS is characterized by excessive bone formation, with syndesmophytes as the major hallmark lesion. Radiographs are considered the gold standard for the assessment of syndesmophytes in AS [1]. For quantification of structural spinal changes in conventional radiographs, the modified Stokes AS spinal score (mSASSS) [2] is currently the best available scoring method based on the OMERACT (Outcome Measures in Rheumatology) filter [3]. For a sufficient sensitivity to change in depiction of structural spinal changes in AS when using conventional radiographs, a minimal observation period of 2 years is required [4]. The mechanisms leading to a pathological new bone formation in AS –a chronic inflammatory disease- are poorly understood. MRI provides an indirect and non-invasive method of investigating

the pathophysiology of new bone formation in AS. Fat deposition can be seen on T1-weighted sequences and bone marrow edema (inflammation) can be seen on T2-weighted sequences with fat suppression, such as the short tau inversion recovery (STIR) sequence [5]. It has been shown in ASSERT study cohort [6] and in other independent cohorts [7–10] that vertebral corners (VCs)/units/edges with inflammation are more likely to develop new syndesmophytes than VCs/units/edges without inflammation. Also, fat deposition in VCs is associated with radiographic progression and this association is stronger than for the presence of inflammation alone [11]. However, this MRI particular sequence of events only partially explained the development of new bone in AS. Other factors may mediate syndesmophyte formation. Osteoporosis is a common complication of AS [12], which can occur because of decreased physical activity and functional capacity related to pain, stiffness, and ankylosis. Low BMD has also been described in patients with early disease [13–15], before any structural changes, suggesting that decreased mobility is not the single mechanism of bone loss. In fact, there is increasing evidence supporting the role of inflammation in bone loss in AS [15–18]. On the other hand, it has also been shown that erosions on radiographs precede the development of a new syndesmophyte at the same site [19]. What leads to simultaneous bone loss and bone formation is still poorly understood. We hypothesize that there could be a causal relationship between MRI inflammation/fat deposition and bone loss at the same vertebral level and also between decreased BMD at a vertebral unit level and subsequent syndesmophyte formation, i.e., low BMD at a vertebral unit level may pathologically enhance repair response of bone.

Thus, the purpose of this study is to investigate the relationship between low BMD and the development of syndesmophytes, 2 years later, in patients with AS. Additionally, we aim to investigate the relationship between bone loss and MRI inflammation/fat deposition at the same vertebral level. Addressing this issues will give us more insight into the process of syndesmophyte formation.

Specific Aims of the Project:

- 1) To assess the relationship between decreased bone mineral density (BMD) and the development of syndesmophytes at the vertebral unit level in patients with ankylosing spondylitis (AS).
- 2) To investigate the relationship between decreased BMD and the MRI vertebral corner inflammation (VCI) and vertebral corner fat deposition (VCFD) at the same vertebral unit level in patients with AS.

More specifically, we aim at understanding whether low BMD at a vertebral unit level (L1, L2, L3, L4, L5) increases the likelihood for the formation of a new radiographic syndesmophyte in the same vertebral unit, 2 years later. Furthermore, we aim to investigate whether baseline MRI inflammation and fat deposition are associated with baseline bone loss in the same vertebral unit.

Addressing this issues will give us more insight into the process of syndesmophyte formation, which may in turn lead to the definition of new treatment strategies for AS patients with the ultimate purpose of preventing structural damage and improving prognosis.

What is the purpose of the analysis being proposed? Please select all that apply.

Other

New research question to analyze predictors of pathological bone formation in AS.

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

For this study, we intend to analyse the same 80% random sample of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT) cohort [20] that we used in our previous analysis [6,11]. Briefly, ASSERT was a 24-week multicenter, randomized, double-blind, placebo-controlled trial with infliximab that included subjects with AS (according to the modified New York criteria), with Bath AS Disease Activity Index [21] (BASDAI) ≥ 4 (range 0–10) and a spinal pain score ≥ 4 (range 0–10), with an open extension until 102 weeks with all patients treated with infliximab. The included patients should have performed a baseline DEXA at the lumbar level, as well as spinal radiographs at baseline and 102 weeks, and a spinal MRI at baseline.

Main Outcome Measure and how it will be categorized/defined for your study:

Of the first analysis, the main outcome is new syndesmophyte formation, as assessed by the individual vertebral corner scores of the modified Stoke AS spine score (mSASSS), changing from a score <2 at baseline to a score ≥ 2 at 2 years of follow-up.

Of the second analysis, the main outcome is the presence of decreased baseline bone mineral density (BMD) at a vertebral level (L1, L2, L3, L4, and L5) assessed by Dual-energy x-ray absorptiometry. Only the baseline BMD scores will be analysed, i.e., the BMD scores of patients not yet treated with infliximab. BMD will be analyzed as a continuous variable.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

Of the first analysis, the main predictor/independent variable is baseline bone mineral density, assessed by Dual-energy x-ray absorptiometry, at a vertebral level (L1, L2, L3, L4, and L5). Only the baseline BMD scores will be analysed, i.e., the BMD scores of patients not yet treated with infliximab. BMD will be analyzed as a continuous variable.

Of the second analysis, the main predictor/independent variable is the presence of MRI vertebral corner inflammation and vertebral corner fat deposition at baseline.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Age (years), gender (males/females), disease duration (years), HLA-B27 genotype (positive/negative), baseline C-reactive protein (CRP) levels (mg/L), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [21] (0-10), Ankylosing Spondylitis Disease Activity Score (ASDAS)[22], presence of syndesmophytes/bridging at baseline (presence of syndesmophytes: mSASSS ≥2; absence of syndesmophytes: mSASSS <2, at the corresponding vertebral corner), baseline MRI vertebral corner inflammation and vertebral corner fat deposition (presence/absence) and treatment with TNFi (yes/no).

Statistical Analysis Plan:

Demographic and baseline disease characteristics (age, gender, disease duration, HLA-B27 genotype, baseline C-reactive protein (CRP) levels, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS), presence of syndesmophytes/bridging at baseline, presence of MRI vertebral corner inflammation (VCI) and vertebral corner fat deposition (VCFD) at baseline and treatment with TNFi) will be summarized using descriptive summary statistics for continuous variables and counts/percentages for categorical variables.

Bone mineral density (BMD) assessment:

Dual-energy x-ray absorptiometry (DEXA) will be used to assess baseline BMD (patients not yet treated with infliximab) at a vertebral unit level (L1, L2, L3, L4, L5). Statistical analyses will be performed considering BMD as a continuous variable.

Radiographic assessment:

The radiographic progression, i.e., the development of syndesmophytes from baseline to week 102 [23] will be evaluated using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) [2,3]. Spinal radiographs were scored by two qualified and well-trained readers, who were blinded to the patient's identity, time order, and treatment. For this study, the individual scores for each of the vertebral corners (VCs) will be used.

MRI assessment:

MRIs were previously scored by two readers at baseline using a VC approach [5]. T1-weighted and STIR sequences were assessed and, the VCs of L1, L2, L3, L4, and L5 were scored for the presence/absence of VCI and VCFD. MRI evaluations were performed according to the methodology applied in our recently published study [11]. The two MRI readers were unaware of the patients' identity, their treatment, the scores of the other imaging modality and the time-order of the images (fully unbiased scores).

Statistical analysis will be performed using SAS. Data will be analyzed at the patient level and at the vertebral unit level in the 5 vertebral units that were assessed by DEXA BMD, mSASSS, and spinal MRI. Frequencies of patients with new syndesmophytes, as well as of the number of new syndesmophytes per vertebral unit will be computed. BMD scores per vertebra will be described. Univariable and multivariable analyses will be performed using a multilevel analysis approach in order to investigate: 1) the relationship between baseline BMD at a vertebral level and the syndesmophyte formation at 2 years and 2) the relationship between baseline BMD at a vertebral level and the presence of MRI VCI and VCFD at the same vertebral level at baseline, according to the above-specified definitions. Generalized estimating equations (GEEs) will be applied making use of all data, across all levels, i.e.

patient level and vertebral unit level [24]. The unit of analysis will be the vertebral corner, and the levels will be “vertebral region” (L1, L2, L3, L4, L5), and “reader”. Multilevel analysis adjusts for within-patient correlation (by vertebral unit level and radiograph/MRI reader, i.e., adjusting for the dependence of observations arising from multiple measurements in different vertebral units of the same patient and also adjusting for the radiograph and MRI readers as another source of dependency of results). Potential confounders will be considered, namely clinical disease activity (BASDAI and ASDAS), CRP, gender, age, disease duration, HLA-B27 status, treatment, presence of syndesmophytes/bridging at baseline and presence of inflammation or fat deposition in MRI at baseline.

In order to conduct this analysis, we need to use baseline DEXA data (raw BMD data, Z- and T-scores, at L1, 2, 3, 4, 5) from the YODA secure data sharing platform and merge these data with the database we already have [6,11] after uploading it to the YODA secure data sharing platform. Our database [6,11] contains demographic and baseline disease characteristics, radiographic mSASSS scores (baseline and 102 weeks) and MRI scores (baseline).

Project Timeline:

Project start date: 01/03/2018

Analysis completion date: 30/05/2018

Date manuscript drafted and first submitted for publication: 15/01/2019

Date results reported back to the YODA Project: 15/01/2019

Dissemination Plan:

Results of this project will be presented at main international conferences in Rheumatology, namely EULAR and ACR. The plan is to present them in 2018/2019. A manuscript will be submitted to a high impact factor journal in the area of rheumatology.

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