

# Utility of magnetic resonance imaging in Crohn's associated sacroiliitis: A cross-sectional study

## Study Protocol

### Study Subjects

This is a cross-sectional study of consecutive subjects prospectively identified and enrolled from an outpatient clinic of Jill Roberts Center for Inflammatory Bowel Disease (IBD) at a tertiary care academic medical center. Subjects between 18 and 65 were enrolled from April 2016 through May 2017 (Figure S1). All subjects met clinical, pathological or radiological criteria for CD. Patients with ulcerative colitis, indeterminate colitis, other inflammatory arthritis (eg, rheumatoid arthritis, systemic lupus erythematosus, psoriatic or reactive arthritis), co-existent autoimmune diseases (eg, celiac disease, Behçet's disease) or skin psoriasis were excluded. All subjects were either biologic naïve or had been off systemic biologics >6 months prior to enrollment and could remain on non-biologic CD therapy (eg, methotrexate, sulfasalazine, azathioprine or 6-mercaptopurine). Patients could also be on vedolizumab, an antagonist of  $\alpha 4\beta 7$  integrin in the intestinal epithelium which has no established efficacy in extra-intestinal manifestations of CD. Other exclusions included malignancy less than 5 years in remission (except for non-melanomatous skin cancer) or having a contraindication to MRI.

### Ethics Committee

Study was conducted according to Good Clinical Practice guideline and was approved by Institutional Review Boards of Hospital for Special Surgery and Weill Cornell Medicine.

### Clinical and Serologic Assessment

After obtaining informed consent, a detailed history was elicited. Subjects reporting back pain were further classified as having IBP if they met ASAS criteria, that is, they fulfilled 4 out of following 5 back pain parameters: onset of symptoms <40 years of age, insidious onset of pain, nocturnal pain, improvement with exercise and no improvement with rest. Subjects with IBP were further classified as having axial SpA according to European Spondylarthropathy Study Group criteria (ESSG) based on IBP plus the underlying CD diagnosis. One investigator (FM) performed a 66-68 joint count, entheses exam (lateral epicondyles of humerus, medial condyles of femur and Achilles tendons), obtained Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Index (ASDAS), and a Harvey Bradshaw index (HBI), a validated measure of CD activity. Peripheral blood was collected for measurement of C-reactive protein (CRP) and cytokine analysis (interleukin [IL]-2, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12/23, IL-17A, IL-17F, IL-21, IL-22,  $\gamma$ -interferon and tumor necrosis factor [TNF]- $\alpha$ ). CRP value was used to calculate ASDAS-CRP (Ankylosing Spondylitis Disease Activity Index-CRP), a validated measure of axial disease activity. Cytokine concentrations in serum were determined using a Legend-plex human Th cytokine 13-plex panel kit (BioLegend) according to the manufacturer's instructions. Data were acquired with a BD LSRII Fortessa flow cytometer (BD Biosciences) and analyzed using the BioLegend's LEGENDplex Data Analysis Software.

## **MRI Protocol**

MRI was performed with 1.5 Tesla clinical imaging units (GE Healthcare, Waukesha, WI, USA) using phased-array coils. Sequences were acquired in a semicoronal plane tilted parallel to the long axis of the SIJ with 3-mm section thickness and 34 slices acquired. Sequences were as follows: T1-weighted spin echo (T1; time to recovery [TR] 500-600 milliseconds, time to echo [TE] 12 milliseconds) and short tau inversion recovery (STIR) fast spin echo (TR 4000-5000 milliseconds, time to inversion 150 milliseconds, effective TE 15-20 milliseconds). All subjects underwent T1 and STIR sequence MRI of SIJ.

## **Evaluation of SIJ MRI**

The semicoronal images were independently read and scored by 2 expert rheumatologists (SJP, UW) and 1 newly trained rheumatologist reader (GK), blinded to any clinical information. SIJ MRIs were evaluated and scored for presence of BME and structural lesions (erosion, fat metaplasia, backfill and ankylosis) using a validated scoring method originally derived from the Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ module. SIJ MRI was considered “positive” for presence of sacroiliitis if it met global evaluation, based on the reader's overall evaluation of presence or absence of sacroiliitis by taking into account the contextual signature of both active and structural SIJ lesions. In addition, we tested whether the following 3 MRI criteria for sacroiliitis were met: (a) ASAS definition of active sacroiliitis; (b) SPondyloarthritis Caught Early (SPACE) proposal, based on presence of erosions and fat metaplasia; and (c) Morpho proposal, based on presence of BME and/or erosion. For analysis, MRI positivity for sacroiliitis was defined based on majority-of-readers agreement ( $\geq 2$  out of 3 readers).

## **Standardized Lesion Definitions on SIJ MRI**

Standardized lesion definitions illustrated by a set of annotated reference images were applied. SIJ lesions were scored binarily as being present or absent per joint quadrant for BME, fat metaplasia and erosion (range 0-8 lesions per MRI slice), or per joint half for backfill and ankylosis (range 0-4 lesions per MRI slice). SI joint quadrants were generated by virtual lines subdividing each SIJ into an upper and lower half on the iliac and sacral side. BME was defined as an increase in bone marrow signal in the subchondral bone on STIR images, fat metaplasia as a focal increased signal in bone marrow on T1SE images. For both lesion types, the center of the sacrum at the same craniocaudal level was used as the primary reference for normal bone marrow signal. Erosion was determined as full-thickness loss of dark appearance of either iliac or sacral cortical bone of the SIJ and change in normal bright appearance of adjacent bone marrow on T1SE images. Normal iliac or sacral marrow on the same slice at the same craniocaudal level served as reference signal. Backfill was defined as bright signal on T1SE sequence within an erosion cavity, demarcated from adjacent bone marrow by an irregular band of dark signal reflecting sclerosis at the border of the original erosion. Ankylosis was defined as bright signal on T1SE images extending across the SIJ.

## **Statistical Analysis**

Descriptive analyses were conducted for all baseline variables and are presented as means or medians for continuous variables and percentages for categorical variables. Differences between groups were quantified using the independent t test (normally distributed data), Mann-Whitney

test (non-normally distributed data) and Chi-square test when appropriate. Mean (SD) and median (interquartile range [IQR]) of SIJ quadrants/halves affected by a given lesion were computed over 3 readers pooled. The frequency of affected SIJ quadrants/halves on subject level and the frequency of MRI evidence for sacroiliitis according to 4 pre-defined MRI classification criteria were described as concordantly reported by the majority ( $\geq 2/3$ ) of readers to enhance specificity. We also calculated the proportion of subjects where all 3 readers agreed that a given SIJ lesion is absent. Agreement between readers for granular SIJ lesions (ie, BME, erosion, ankyloses, fat metaplasia and backfill) was calculated by intraclass correlation coefficient (ICC), two-way random effects, single measure, absolute agreement definition, for all readers together and for the 3 possible reader pairs separately. ICC values of  $<0.50$ ,  $<0.75$ ,  $\leq 0.90$ , and  $>0.90$  were considered to reflect poor, moderate, good, and excellent reproducibility, respectively. Furthermore, kappa ( $\kappa$ ) statistics were utilized to determine agreement between readers for dichotomous outcomes of 4 definitions of MRI positivity. Kappa agreement was categorized according to Landis and Koch:  $<0$  = no agreement, 0.00-0.20 = slight, 0.21-0.40 = fair, 0.41-0.60 = moderate, 0.61-0.80 = substantial and 0.81-1.00 = perfect. S IJ M RI of 71 patients from an unrelated axial SpA inception cohort (24 subjects with active ankylosing spondylitis, 23 subjects with both IBD and ankylosing spondylitis and 24 subjects with non-specific back pain) served to determine reader agreement in a calibration sample with a relatively high frequency of the 5 SIJ lesions under consideration. SPSS Statistics, Version 25.0 (IBM, Armonk, NY, USA) was used to perform statistical analysis.