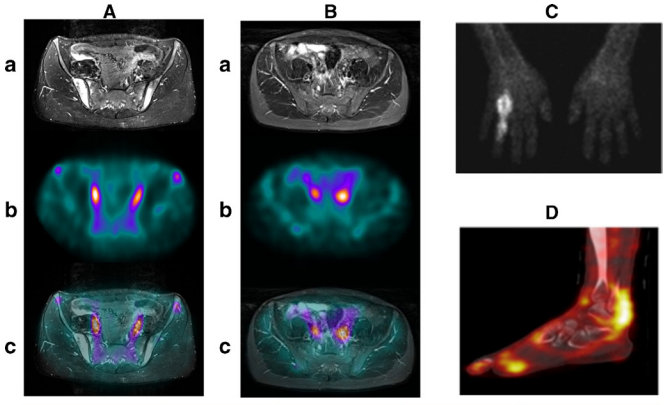
Immunoscintigraphy in axial spondyloarthritis: a new imaging modality for sacroiliac inflammation

Imaging of sacroiliac joints (SIJ) is one of the cornerstones in early recognition of axial spondyloarthritis (axSpA).[1] Currently, MRI is the preferred technique to visualise bone marrow oedema (BME), which can be defined as sacroiliitis when certain criteria are met.[2] However, the definition of sacroiliitis as being 'highly suggestive for axSpA' has limitations in situations when BME is subtle or when SpA-like BME lesions are present due to other conditions such as mechanical stress.[3 4] This underscores the need for additional and more specific imaging modalities. Given the marked efficacy of tumour necrosis factor (TNF) inhibitors in axSpA, with approximately 50% of patients achieving a clinically important response,[5] we reasoned that molecular imaging studies aiming at selectively visualising TNFα in vivo at the site of clinical inflammation could be an attractive approach. Therefore, we set up a proof-of-concept study in axSpA patients by performing scintigraphy with Tc99m-labelled certolizumab pegol (CZP) as tracer. We investigated the agreement between tracer uptake on immunoscintigrapy and BME on MRI at the same localisation of the SIJ. CZP was conjugated with succinimidyl-6-hydrazino-nicotinamide (S-HYNIC), a bifunctional crosslinker. Subsequently, solutions of 1.25 mg conjugated S-HYNIC CZP were used to radiolabel with Tc99m. Seven axSpA patients (71.4% male; mean age 36±5.7 years; mean disease duration 9.3±4.8 years) were intravenously injected with 740 MBq Tc99m-radiolabelled CZP (10.6 MBq/kg) in a similar way as in a classical bone scintigraphy procedure. Static images with single photon emission tomography (SPECT)/CT of SIJ were acquired 4–6 hours postinjection. No procedure-related adverse events were observed. Of note, all patients had high disease activity (mean ASDAS 3.5±0.7) and five out of seven patients failed on at least one TNF inhibitor at inclusion. Uptake of tracer was scored semiquantitatively, per SIJ quadrant: 0=no uptake, 1=faint uptake or 2=clear uptake. BME on MRI was scored per SIJ quadrant according to the SPARCC method including depth and intensity scores.[6] Agreement between MRI–SIJ and immunoscintigraphy was calculated (kappa; percentage agreement) for all quadrants separately using a cut-off of ≥1 for MRI as well as for immunoscintigraphic scores.



	BME & tracer uptake	BME & no tracer uptake	no BME & tracer uptake	no BME & no tracer uptake
Patients, n (%)	5 (71.4%)	0	0	2 (28.6%)
Quadrants, n (%)				
Right upper iliac quadrant	3 (42.9%)	1 (14.3%)	0	3 (42.9%)
Right upper sacral quadrant	2 (28.6%)	1 (14.3%)	0	4 (57.1%)
Right lower sacral quadrant	2 (28.6%)	1 (14.3%)	1 (14.3%)	3 (42.9%)
Right lower iliac quadrant	5 (71.4%)	0	0	2 (28.6%)
Left upper iliac quadrant	3 (42.9%)	0	0	4 (57.1%)
Left upper sacral quadrant	1 (14.3%)	1 (14.3%)	0	5 (71.4%)
Left lower sacral quadrant	2 (28.6%)	0	0	5 (71.4%)
Left lower iliac quadrant	3 (42.9%)	0	0	4 (57.1%)

Figure 1 (A,B) MRI and immunoscintigraphy of the sacroiliac joints after administration of Tc99m-radiolabelled certolizumab pegol in a patient with active axial spondyloarthritis (A) and in one with partial ankylosis (B). (a) MRI STIR sequence visualising extensive bone marrow oedema at both sacroiliac joints (A) and no bone marrow oedema (B). (b) Distribution of Tc99m-radiolabelled certolizumab pegol in sacroiliac joints 4–6 hours postinjection depicting clear uptake (A) and no uptake (B). (c) Fusion of the MRI and immunoscintigraphic SPECT image. (C) Immunoscintigraphic image 4–6 hours postinjection of Tc99m-radiolabelled certolizumab pegol of hands of a patient with axial spondyloarthritis with concomitant clinically dactylitis of the fourth digit depicting marked tracer uptake in both the joints and the accompanying flexor tendon of that digit. (D) SPECT-CT 4–6 hours postinjection of Tc99m-radiolabelled certolizumab pegol of the right foot in a patient with spondyloarthritis and concomitant enthesitis of the Achilles tendon depicting distinct tracer uptake at the insertion of the Achilles tendon. Below: Table with agreement on the presence of BME on MRI–SIJ and tracer uptake on the immunoscintigraphy at patient level and at quadrant level. BME, bone marrow oedema; SPECT, single photon emission tomography; STIR, short tau inversion recovery.

A mean score of 12.9±13.2 BME lesions and a mean score for tracer uptake on immunoscintigraphy of 4.86±5.4 were found. Figure 1 shows the distribution of BME on MRI–SIJ and tracer uptake on immunoscintigraphy together with the fusion image of MRI and SPECT. Two out of seven patients had no BME on MRI and also no tracer uptake on scintigraphy. Interestingly, one of those presented with a partial ankylosis of the SIJ, suggesting that in vivo detection of TNF does not correlate with bone formation (figure 1). The agreement between tracer uptake and MRI–SIJ BME was good for all quadrants separately (figure 1). When taking all quadrants in consideration, we found a good correlation (kappa=0.82; total agreement=91.1%). Clear tracer uptake (score 2) was correlated with deep BME lesions on MRI–SIJ with a Spearman's rho correlation of 0.986 ($p<0.00$) and 0.956 ($p<0.00$) for left and right SIJs, respectively.

At present, there is no agreement on the minimum BME size necessary to be defined as 'positive' but our study suggests that 'deep' BME lesions on MRI–SIJs are more suggestive of axSpA. Taking these extended lesions into account, very high agreement between tracer uptake and MRI–SIJ BME lesions was found. Notwithstanding the study's limitations (low sample size and lack of a control group), in an era of evidence-based medicine, there is still an unmet need to determine whether observed BME on MRI is caused by underlying cytokine-driven inflammation which can be visualised by this immunoscintigraphic approach. This findings support a more rational approach of determining the most appropriate biological treatment for an individual patient.

In summary, our study showed the presence of TNF-driven active disease in SIJs in axSpA patients by using a non-invasive immunoscintigraphic technique with radiolabelled CZP. Especially with deep BME lesions on MRI–SIJ, agreement with tracer take-up was excellent.

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