The early spondyloarthtiris (ESPA): Concept, role of new imaging techniques, therapeutic opportunities and research agenda

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Abstract
Introduction
The interest on early Spondyloarthritis (eSpA) is born in the last ten years for the acknowledgment of the “evidence based” utility of the rapid diagnostic and therapeutic approach in this disease. The aim of this review was to discuss early spondyloarthtiritis in detail.

Discussion
The chronological definition of eSpA is not uniform in literature. ASAS criteria, together with the use of MRI and US in early diagnosis have increased the diagnostic power and the capacity to diagnose eSpA. Few issues investigated and codified the use of DMARDs and antiTNFalpha in early phases.

Conclusion
Future studies must be conducted in the future to better clarify MRI and US in early diagnosis. The capacity to classify eSpA. Few efficacies strategies to stop clinical and radiological progression, have deeply changed our point of view of the mission in rheumatology.

In the first 10 years of disease, the axial and peripheral damages might be deeply modified with antiTNFalpha treatment1. After this first window of opportunity, the clinical efficacy of the therapy dramatically decreased.

Unfortunately, the diagnostic delay (DD) is still very high2 with important consequence on radiological damage (New York score for sacroiliitis and bamboo spine).

Furthermore, since the phases of the disease, the disease might have severe outcomes on quality of life of patients in terms of depression and anxiety3.

The aim of this review was to discuss the concept, role of new imaging techniques, therapeutic opportunities and research agenda of early spondyloarthtiris.

Method
We firstly discussed the definition of eSpA: the chronological cut off, the concept of undifferentiated SpA (uSpA), the new ASAS classification criteria, the role of new imaging techniques in diagnosis (Ultrasound [US] and Magnetic resonance [MRI]), and the actual therapeutic approach with disease modifying drugs (DMARDs and antiTNFalpha) in early disease, from the most recent issues of literature (until June 2013).

Discussion
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Definition of eSpA
Chronological definition
On the term “early”, there is a great discordance and none definition was definitely accepted or validated in literature. For eSpA, De Miguel4 and D’Agostino5 proposed a chronologic limit since the onset of symptoms of 24 months4, with a successive follow up of 2 years to confirm diagnosis, while, previously, only in early Psoriatic Arthritis (ePsA), Lindqvist6, Scarpa et al.7 and Bandinelli8 suggested three different definitions: less than 2 years, 12 weeks and 1 year, respectively.

The concept of undifferentiated SpA (uSpA) and axial SpA of new ASAS criteria
Before the introduction of ASAS criteria in 20099, making the diagnosis of axial SpA at an early stage was difficult and highly dependent on clinical experience and intuition of the treating physician, overall for the difficulty to use traditional X-rays for diagnosis in this phase.

Before the introduction of the ASAS criteria, the term “undifferentiated SpA” (uSpA) was created for patients with clinical features for SpA, not fulfilling the previous classification criteria, mainly when sacroiliitis was not detectable on x-rays. Thus, uSpA was not considered an important part of the natural history of the disease but a clinical entity shared from the other SpA subtypes.

Recently, Rudwaleit et al. assessed new diagnostic criteria for inflammatory back pain (IBP) and introduced MRI as

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diagnostic device to individuate early sacroiliitis.

In fact, the patients with normal sacroiliac joints (SJJ) on X rays but with the presence of bone oedema at MRI were defined as axial spondyloarthritis that should be considered a pre-radiographic disease continuum of Ankylosing Spondylitis.

**New Classification criteria for early SpA ASAS**

The new ASAS 2009 criteria are based on a combination of symptoms IBP, HLA B27 positivity and MRI findings that might include uSpA and all previous classification of inflammatory SpA.

In 2010, the update of ASAS/EULAR showed that every expert agreed that in the pre-radiographic (axial) eSpA, with MRI sacroiliac bone oedema, the management recommendations of SpA, included antiTNFalpha, should be equally extend.

Otherwise, it’s also recognized that not all patients with axial eSpA will necessary develop structural radiological damage changes, comprised in criteria for AS.

In previous issues, Colour Doppler was employed to evaluate SJJ, in eSpA patients, erosions were found in 80% and 50% respectively.

Furthermore, in the first issue, sclerosis and fat deposition were present in 71% and 63% of cases.

Probably, the structural damage of the SJJ, not detect by x-ray, might be revealed by MRI, in very early disease, but the exact significance of this datum and its weight on the diagnosis and chose of treatments was not investigated.

**Role of new imaging techniques (MRI and US)**

**MRI**

In early disease, the use of MRI as a diagnostic tool is a very important step because it can reveal pre-radiographic disease. There are four MRI findings of active (acute) sacroiliitis associated with axial SpA: osteitis/bone marrow oedema, enthesitis, capsulitis, and synovitis.

However, the ASAS consensus included only the presence of bone marrow oedema (Figure 1) on STIR sequences and osteitis on the T1 weighted gadolinium as the fundamental feature of sacroiliitis.

Even if STIR sequences at MRI (T2 with fat suppression) might be considered sufficient for early diagnosis to detect bone oedema, in doubt cases, the use of gadolinium (T1 with fat suppression and contrast) seemed more useful to better enhance hyperintensity of signal and to show the increase of perfusion of bone (osteitis).

Otherwise, ASAS committee did not include other active signs of sacroiliitis as synovitis, enthesitis and capsulitis in diagnostic criteria, that probably should be better studied in the future to understand its potential role in early diagnosis.

Chronic structural lesions (bone marrow fat deposition, erosions, sclerosis, ankylosis) have until now an uncertain diagnostic significance; in particular, fat accumulation and erosions might be deeply studied in the future to understand if they might be interpreted as inflammatory and as severity signs, respectively.

In fact, in the Puhakka14 and Weber15 studies, in eSpA patients, erosions were found in 80% and 50% respectively.

**US**

- US of SJJ ultrasound (US) is a routine procedure for joint evaluation and peria rticular ligaments of SJJ evaluation in SpA.

The SJJ effusion in SpA were previously studied by Spadaro et al. and Bandinelli that demonstrated that SJJ effusion at US was more sensitive that clinical SJJ examination, either in definitive SpA or in early SpA.

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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Nevertheless, so far very few papers on US evaluation of the SIJ have been published, overall on tendons assessment, even though it has been well demonstrated that pathological changes could be detected with this diagnostic tool.

In particular, interestingly, Bandinelli et al. in 23 early SpA demonstrated that sacrotuberosous ligament thickness was higher than in controls but a larger cohort of patients might be studied in the future to confirm the importance of ligaments evaluation in eSpA.

- US of entheses and the concept “sub clinical” and “occult enthésitis” in eSpA In 2011, De Miguel et al. found a high sensitivity (53.1%) and specificity (83.3%) of entheses US in 113 early SpA compared to non inflammatory controls and other rheumatic disease.

In the same year, D’Agostino et al., demonstrated in a prospective study on 118 eSpA, that Power Doppler US (PDUS) had a good predictive value of (sensitivity 76.5% and specificity 81.3%) for diagnosis of definitive Spa but did correlate with ASAS criteria.

This datum confirmed that a limit of these criteria is not to include enthesal evaluation as one of the most important features for diagnosis, but probably the presence of numerous scores in literature with not an univocal technique represent until now a great difficulty to a great diffusion of US of entheses in daily practice and its standardization.

Furthermore, enthesis might be often under-diagnosed and showed in early phase by clinical examination only in a small percentage, as Bandinelli et al.8 showed in 92 eSpA patients (Figure 2). In fact, in this study, US showed in high percentage enthesal abnormalities independent from clinical examination and rheumatologic symptoms. The most relevant findings revealed by US were thickness and PDUS signal of entheses, probably due to the oedema, increase of vessels and cell infiltration, respectively, described by Mc Gonagle in initial phase of SpA, even if until now a direct comparison between US and histological data was never performed in humans.

Interestingly, other recent studies showed the presence of “occult” enthesal abnormalities in psoriasis21,22,23 and in inflammatory bowel disease (IBD)24, without signs and symptoms of SpA and without correlation with the activity indices of disease neither of psoriasis neither of bowel.

Actually, there is not a clear definition of this “iceberg disease” and we did not know if might be a disease continuum with eSpA and if these occult abnormalities might have a role on the choice of disease modifying treatments for comorbidities (such severe psoriasis or IBD).

### Treatment

The 2011 international recommendation (with the interview of 1246 rheumatologists of 18 countries) suggested the use of antiTNFalpha also in preradiographic axial disease diagnosed with ASAS criteria (expert agreement of 86%)11. Otherwise, there is still now not a clear definition on the right moment to start a disease modifying treatment in early disease.

Only Scarpa in 2008 conducted a study on effect of traditional DMARDs in eSpA: 35 ePsA treated for six months with low dosage of methotrexate (10 mg weekly) were followed up with routine clinical and laboratory examination25.

The he use of other DMARDs (such salazopyrin and leflunomide) was not investigated.

Only the antiTNF were evaluated in large clinical trials and seemed to be able to determine both clinical and instrumental remission, with impressive effect of bone oedema and osteitis at MRI evaluation in the early phase of disease26,27.

Furthermore, Naredo et al. demonstrated that the US abnormalities (in particular PDUS signal) of entheses were significantly reduced during antiTNFalpha treatment28.

Successively, also Bandinelli showed a clinical case of tight control US of a patient with ePsA treated with antiTNFalpha, with remission of synovitis and dactylitis and microerosion repair29. Otherwise, other studies on the use of US in follow up might be conducted in the future to evaluate its usefulness in monitoring the efficacy of the treatments in eSpA.

### Conclusion

ASAS criteria, together the use of MRI and US in early diagnosis have increased the diagnostic power and the capacity to classify Spa but further studies must be conducted in the future to better clarify MRI and US findings in early phase. An larger research on efficacy of DMARDs and antiTNF treatments in early phase with prospective studies, supported by imaging, are needed in the future.

Furthermore, we proposed for future research agenda to investigate:
- the role on diagnosis of erosions, sclerosis and fat deposition in SIJ at MRI
- the evolution of occult disease in natural course of SpA and its consequence on treatments chose
- the efficacy of treatments (DMARDs and antiTNFalpha) in early Spa patients supported by imaging, with prospective studies

### References

3. Bandinelli F, Prignano F, Bonciani D. Clinical and socio-demographic factors

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