Joint Bone Spine 82 (2015) 411–416

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

Sodium ^{18}F-sodium fluoride PET failed to predict responses to TNFα antagonist therapy in 31 patients with possible spondyloarthritis not meeting ASAS criteria

Christelle Darrieutort-Laffite[a], Catherine Ansquer[b], Yves Maugars[a], Benoît Le Goff[a], Françoise Bodere[b], Jean-Marie Berthelot[a,*]

[a] Service de rhumatologie, Hôtel-Dieu, CHU de Nantes, 1, place Alexis-Ricordeau, 44093 Nantes cedex 01, France
[b] Service de médecine nucléaire, Hôtel-Dieu, CHU de Nantes, 44093 Nantes cedex 01, France

ARTICLE INFO

Article history:
Accepted 23 January 2015
Available online 1 October 2015

Keywords:
Spondyloarthritis
Diagnosis
ASAS
Bone scan
PET
Sodium fluoride
TNFα antagonist

ABSTRACT

Objectives: To determine whether ^{18}F-NaF positron-emission tomography (PET) contributes to the diagnosis of spondyloarthritis and whether observed uptakes predict the response to TNFα antagonist therapy.

Methods: We studied patients who had suspected spondyloarthritis but did not meet ASAS criteria and who were referred for an assessment of eligibility for TNFα antagonist therapy. ^{18}F-NaF PET was offered instead of bone scintigraphy. TNFα antagonist therapy was given if the clinician's level of confidence in the diagnosis of spondyloarthritis based on ^{18}F-NaF PET findings was ≥ 50/100.

Results: Thirty-one patients accepted to undergo ^{18}F-NaF PET. Their mean age was 39.9 ± 11.7 years; 22% were HLA-B27-positive and none had evidence of sacroiliitis by magnetic resonance imaging. Of the 31 patients, 30 had abnormal ^{18}F-NaF PET findings. However, of the 312 high-uptake foci, only 123 (39.4%) matched sites of pain. TNFα antagonist therapy was given to 16 patients. The treated group and untreated group (n = 15) were not significantly different for the mean number of high-uptake foci per patient (11.7 ± 8.1 vs. 8.3 ± 5.1, respectively) or for the proportion of patients with high uptake by the sacroiliac joints (13/16 [81%] vs. 8/15 [53%], respectively). In the treated group, 5 patients met ASAS response criteria after 3 months. These 5 patients were among the 9 treated patients who met Amor's modified criteria (arthritis instead of asymmetrical oligoarthritis). In the 5 responders, the ^{18}F-NaF uptake scores were nonsignificantly lower than in the 11 nonresponders (9.0 ± 8.5 vs. 13.0 ± 6.4, respectively). In the patients for whom the ^{18}F-NaF PET findings increased the level of confidence in the diagnosis of spondyloarthritis, this effect was short-lived.

Discussion: The positive predictive value of ^{18}F-NaF PET for diagnosing spondyloarthritis or predicting a response to TNFα antagonist therapy seems very low. This finding is probably ascribable to poor specificity.

A definitive diagnosis of spondyloarthritis [1] is among the eligibility criteria for TNFα antagonist therapy in patients who respond poorly to nonsteroidal antiinflammatory drugs (NSAIDs) [2]. However, objective signs of spondyloarthritis are often lacking, particularly early in the disease. The new ASAS classification criteria for recent-onset spondyloarthritis [3] are less than ideal. Thus, their specificity in everyday practice seems lower than the 83% reported in the validation study [3], in part because they can misclassify mechanical sacroiliac joint (SIJ) abnormalities as sacroiliitis [4]. Furthermore, the ASAS criteria are not effective in selecting very good responders to TNFα antagonist therapy: in the ABILITY-1 trial, only 36% of the 91 patients given adalimumab had a good response after 3 months, compared to 15% of the 94 patients given a placebo [5]. On the opposite, some patients who have clinical features that strongly suggest spondyloarthritis, particularly multifocal enthesopathy, fail to meet ASAS criteria. Consequently, attention has been directed to new diagnostic tools. Technetium-99m (^{99m}Tc) bone scintigraphy has been found to lack sensitivity and specificity for detecting spinal and SIJ involvement in patients with early axial spondyloarthritis [6]. Nevertheless, this investigation is widely used to look for objective evidence of peripheral or thoracic arthritis/enthesitis [7] or for aseptic osteitis. Another

* Corresponding author.
E-mail address: jeanmarie.berthelot@chu-nantes.fr (J.-M. Berthelot).

http://dx.doi.org/10.1016/j.jbspin.2015.08.012
1297-319X/

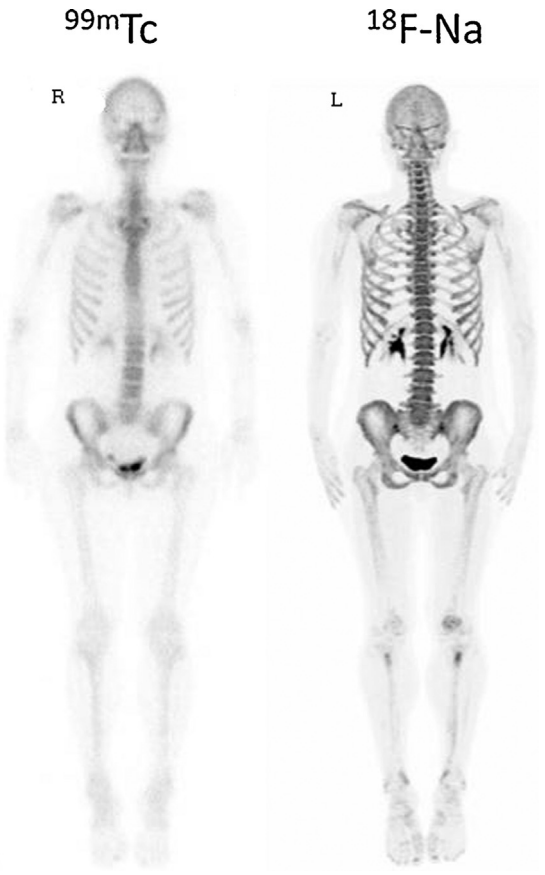

Fig. 1. Example of images obtained by ^{18}F-NaF PET (right) and conventional bone scintigraphy (left) (different patients). Note: ^{18}F-NaF PET shows high-uptake foci in the tibial tuberosities, left patella, and malleoli.

tool is ^{18}F-sodium fluoride (^{18}F-NaF) positron emission tomography (PET) (Fig. 1), which has been used since 1968 to investigate the bone [8]. ^{18}F-NaF PET was more sensitive than ^{99m}Tc scintigraphy for identifying bone metastases [9] and was sensitive for detecting enthesitis [10] or sacroiliitis [11]. ^{18}F-NaF PET is recommended for the diagnosis of osteoarticular abnormalities, including inflammatory diseases [12]. This fact raises the possibility that ^{18}F-NaF PET may perform better than ^{99m}Tc scintigraphy in diagnosing some forms of recent-onset atypical spondyloarthritis. The better sensitivity of ^{18}F-NaF PET may prove beneficial provided the findings are sufficiently specific of spondyloarthritis, particularly as ^{18}F-NaF PET and magnetic resonance imaging (MRI) detect different abnormalities of the SIJ (i.e., are not redundant with each other) [13].

In this study, our objective was to assess the potential diagnostic usefulness of ^{18}F-NaF PET in patients who were eligible both for ^{99m}Tc scintigraphy, because of suspected spondyloarthritis with failure to meet ASAS criteria; and for an assessment of the appropriateness of TNFα antagonist therapy [14], because of an inadequate response to NSAIDs. Over a 1.5-year period, consecutive patients in this situation were given detailed information on ^{18}F-NaF PET and ^{99m}Tc scintigraphy. Those who consented to ^{18}F-NaF PET instead of ^{99m}Tc scintigraphy were included in the study, and their 3-month outcomes were assessed. All patients were evaluated by the same rheumatologist who used a 100-mm scale to rate the level of confidence in a diagnosis of spondyloarthritis based on the ^{18}F-NaF PET findings. Patients with a confidence score ≥ 50/100 were given a trial of TNFα antagonist therapy, and their response was evaluated. This pragmatic study was designed both to determine whether ^{18}F-NaF PET increased the rheumatologist's confidence in the diagnosis of spondyloarthritis and whether ^{18}F-NaF PET identified patients who responded well to TNFα antagonist therapy despite not meeting ASAS criteria [3].

1. Methods

1.1. Patients

We prospectively identified consecutive patients who were referred to a single hospital-based rheumatologist between May 2011 and December 2012 for an assessment of eligibility for TNFα antagonist therapy and who met the following criteria: diagnosis by a rheumatologist of possible or probable spondyloarthritis; failure to meet ASAS criteria, with absence of suggestive SIJ abnormalities by radiography and MRI; eligibility for further diagnostic evaluation by ^{99m}Tc scintigraphy; and no contraindication to TNFα antagonist therapy. After receiving detailed information on ^{18}F-NaF PET and ^{99m}Tc scintigraphy, these patients were asked whether they consented to undergo ^{18}F-NaF PET instead of ^{99m}Tc scintigraphy. Those who consented were included in the study and underwent standardized evaluations at baseline (first visit, during which ^{18}F-NaF PET was offered as an alternative to ^{99m}Tc scintigraphy) and after the ^{18}F-NaF PET results were available (post-PET visit). Patients whose ^{18}F-NaF PET findings led to a diagnosis of spondyloarthritis with a confidence rating ≥ 50/100 were started on TNFα antagonist therapy then evaluated 3 months later (post-TNFα antagonist visit). At each visit, the following data were recorded: tender and swollen joint counts on 28 joints, pain score on a visual analog scale (VAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Ankylosing Spondylitis Disease Activity Score (ASDAS). We also recorded the Widespread Pain Index (WPI) and the Symptom Severity score (SS) for fibromyalgia [15]. The serum C-reactive protein (CRP) level and HLA-B27 status were noted.

The rheumatologist used two 100-mm VASs to self-evaluate the level of confidence in the diagnosis of spondyloarthritis (0: no confidence at all; 100: complete confidence) and the appropriateness of a trial of TNFα antagonist therapy. These scales are highly sensitive to change and have been used previously in studies of patients with suspected spondyloarthritis [16,17]. They were completed at the end of each visit, as well as at the beginning of the post-PET visit after reading the PET results (Table 1). If both VAS scores were ≥ 50 at the end of this post-PET visit, TNFα antagonist therapy was offered. A good treatment response at the post-TNFα antagonist visit 3 months later was predefined as a BASDAI lower than 40/100 or an at least 50% improvement in symptoms compared to the post-PET visit. The modified Amor's criteria [18] were assessed retrospectively after replacing the "asymmetric oligoarthritis" criterion (2 points) by "arthritis".

1.2. ^{18}F-NaF PET

^{18}F-NaF PET was performed within a few weeks after the baseline visit. The patients were not asked to stop their antiinflammatory medications. The PET machine was a BioGraph® 40 mCT (Siemens Lenoxville, PA, USA). The radiotracer Flucis® (Cisbio International, Bagnol/Ceze, France) was injected into a cubital-fossa vein in a dose of 3 MBq/kg. PET images were acquired 30 to 60 minutes (mean: 44.3 ± 9.4) after the injection. All ^{18}F-NaF PET scans were read and scored by the same senior nuclear medicine physician who was unaware of the diagnosis. All foci of increased uptake at joints and entheses were described. In the patients given TNFα antagonist therapy, at the end of the 3-month visit, the ^{18}F-NaF PET scans were reevaluated with knowledge of the clinical data to determine whether the high-uptake sites matched the symptomatic sites at