Clinical significance of abdominal scintigraphy using ^{99m}Tc-HMPAO-labelled leucocytes in patients with seronegative spondyloarthropathies

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Received 25 June and in revised form 10 September 2000 / Published online: 4 November 2000

Abstract. Abdominal scintigraphy shows silent gut inflammation in patients with spondyloarthropathies (Sp) without clinical evidence of gut inflammation. Abdominal scintigraphy images are different than those obtained in patients with ulcerative colitis or Crohn's disease and are not related to the anti-inflammatory drugs administered. The aim of this study was to examine the clinical associations of findings on abdominal scintigraphy in patients with Sp. A total of 204 Sp patients (European Spondylarthropathy Study Group 1991 criteria) and 54 non-Sp controls receiving non-steroidal anti-inflammatory drugs were studied. Abdominal scintigraphy images were obtained at 30 and 120 min after injection of technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HMPAO)-labelled leucocytes. ^{99m}Tc-HMPAO-labelled leucocyte scans were positive in 104 Sp patients (50.9%) and in six non-Sp controls (2.9%) (P<0.001; OR=8.32; 95% CI=3.23–22.67). Silent gut inflammation was not associated with any of the following: age of onset, duration of evolution, sex, family history of Sp or psoriasis, articular manifestations, extra-articular manifestations, radiological findings or HLA-B27 positivity. Positive abdominal scintigraphy was associated with active disease (P<0.0001; OR=52.7; 95% CI=19–145.6) and an increase in the C-reactive protein (P<0.005; OR=3.4; 95% CI=1.5–7.4). It is concluded that (a) abdominal scintigraphy using ^{99m}Tc-HMPAO-labelled leucocytes is of value in detecting the silent gut inflammation in Sp patients, and (b) silent gut inflammation is related to the clinical activity, but is not associated with any particular type of illness or with HLA-B27.

Keywords: Silent gut inflammation – ^{99m}Tc-HMPAO-labelled leucocyte scintigraphy – Abdominal scintigraphy – Spondyloarthropathy

Eur J Nucl Med (2000) 27:1768–1773
DOI 10.1007/s002590000393

Introduction

Spondyloarthropathies (Sp) are inflammatory multisystemic diseases that present with rheumatoid factor and rheumatoid nodules, association with HLA-B27, lower limb oligo-arthritis, enthesitis, sacro-iliitis with or without spondylitis and a family history of Sp. Extra-articular manifestations can be present and generally are secondary to gastrointestinal, genitourinary, ocular or skin inflammation [1]. In patients with Sp, microscopic lesions similar to the lesions found in patients with inflammatory bowel disease (IBD) have been demonstrated, even when symptoms of ulcerative colitis or Crohn's disease are not present [2]. Inflammation of the target organs (joints, tendons and eyes) is probably related to an increase in gut permeability and a defect in immunological defence mechanisms. These alterations can produce antigen-antibody complexes or immune reactions by T cells [3, 4].

The method used to date to demonstrate silent gut inflammation in patients with Sp has been ileocolonoscopy with biopsy [2]. This method is invasive, produces problems for patients and usually is rejected by patients because of the absence of intestinal symptoms. In addition, the interpretation of histological findings can be confusing. Abdominal scintigraphy is a sensitive method, is easier to perform than ileocolonoscopy and is well accepted by the patient. In a previous study that we performed, abdominal scintigraphy using technetium-99m hexamethylpropylene amine oxime (^{99m}Tc-HMPAO)-labelled leucocytes detected silent gut inflammation in 53% of patients with active Sp without clinical evidence of IBD. The pattern of gut tracer uptake was different to that in patients with ulcerative colitis or Crohn's disease [5]. Positive abdominal scintigraphy was not related to non-steroidal anti-inflammatory drugs (NSAIDs) and was more frequent when inflammatory spinal pain was

present (though the number of such cases was small). In our previous work we described the link between Sp and silent gut inflammation, but given the low number of patients we could not draw firm conclusions as to the clinical significance of these findings [6]. Recently, a relationship between abdominal scintigraphy and intestinal histological findings has been suggested [7]. The clinical significance of these data is unknown.

In this work we studied the clinical associations of findings on abdominal scintigraphy using ^{99m}Tc-HMPAO-labelled leucocytes in a large group of patients with Sp.

Materials and methods

Patients and controls. Two hundred and four patients fulfilling the criteria for Sp proposed by the European Spondylarthropathy Study Group (ESSG) in 1991 [1] were recruited in the rheumatology outpatient clinic. Patients with past or present symptoms and signs of IBD were excluded. A group of 54 individuals without Sp agreed to participate in the study as a control group. All of these patients were studied by scintigraphy based on clinical suspicion of focal sites of extra-abdominal infection. This study was approved by the Hospital Ethics Committee. All control patients were receiving NSAIDs at the time of the study.

Clinical and radiological data were obtained during the 15 days preceding scintigraphy. They included: family history of Sp, articular manifestations (axial inflammation, arthritis and enthesitis), extra-articular manifestations (uveitis, conjunctivitis, oral ulcers, genital ulcers, erythema nodosum, balanitis circinata, psoriasis, keratoderma blennorrhagica and urethritis), radiological findings (sacro-iliitis, syndesmophytes and erosions) and previous treatments. C-reactive protein (CRP) was determined in 108 patients by nephelometry (normal value >0.5). Clinically active disease was defined as the presence of axial inflammation, synovitis or enthesitis.

Leucocyte labelling. In vitro leucocyte labelling was performed according to the method of Vorne et al. [8] and Blasco et al. [9] with some modifications [5, 6]. Briefly, a 40-ml sample of peripheral blood was taken up in a syringe containing 7.5 ml of acid citrate dextrose used as anticoagulant. After spontaneous sedimentation of red cells for 1 h at room temperature, the supernatant was aspirated and centrifuged in sterile tubes at 150×*g* for 15 min, and the mixed leucocyte pellet was then collected. A 10-ml sample of peripheral blood was centrifuged at 2000×*g* for 10 min to obtain cell-free autologous plasma.

The ^{99m}Tc-HMPAO complex was formed by adding 1110 MBq of free technetium (pertechnetate) in 5 ml isotonic saline to a commercial kit containing HMPAO (Nycomed-Amersham). The cell pellet was incubated for 30 min at room temperature, in 2 ml of autologous plasma and 2 ml of ^{99m}Tc-HMPAO complex. Following incubation, the unbound ^{99m}Tc-HMPAO was removed by centrifugation at 150×*g* for 10 min. Cells were washed out and resuspended in 4 ml of plasma, and re-injected intravenously. The mean injected dose was 220 MBq (6 mCi).

Imaging and interpretation. Scintigraphy was performed using a large-field-of-view gamma camera, equipped with a low-energy, parallel-hole collimator (Orbiter 75, Siemens). Images were obtained in the anterior abdominal projection at 30 min and 2 h after leucocyte re-injection, and 600 kcounts were accumulated for each image. Craniocaudal, right and left oblique and pelvic outlet views were acquired to localise tracer uptake when necessary. Two nuclear medicine physicians without knowledge of the clinical history independently evaluated the scintigraphic images. Any intestinal uptake was interpreted as a positive study when areas of increased abnormal concentration of the tracer were seen in the early images and remained similar or became more intense in subsequent images. Tracer uptake was scored from 1 (lowest uptake) to 4 (highest uptake) based on comparison with iliac crest uptake: 1 = higher than background, 2 = lower than iliac crest uptake, 3 equal to iliac crest uptake and 4 = higher than iliac crest uptake. The bowel was divided into five segments (rectosigmoid, descending colon, transverse colon, ascending colon, and terminal ileum and small intestine). Tracer uptake lower than 2 was considered as a negative study.

Statistical analysis. Data were analysed using the chi-square test with Yates correction when appropriate, Fisher's two-tailed exact test, the Wilcoxon signed ranks test, odds ratios (OR) and 95% confidence intervals (CI) (SPSS program). A value of $P<0.05$ was considered statistically significant.

Results

Of the 204 Sp patients studied, 125 (61.2%) were male. Ankylosing spondylitis was the diagnosis in 105 (51.47%), Reiter's syndrome or reactive arthritis in 19 (9.31%), psoriatic arthritis in 26 (12.7%) and undifferentiated Sp in 54 (26.4%). Mean age at the onset of disease was 36.9 years (range 1–47). Seventy patients had a family history of Sp or psoriasis. Eighty-two (40.2%) patients had oligo-arthritis, 26 (12.7%) polyarthritis and 9 (4.4%) monoarthritis. One hundred and nine (53.4%) patients had enthesitis.

Extra-articular manifestations consisted of conjunctivitis in 29 patients (14.2%), urethritis in 28 (13.7%), psoriasis in 26 (12.7%), acute diarrhea without blood at the onset of the disease in 33 (16.1%) and uveitis in 17 (12.1%). HLA-B27 was positive in 86 of the 195 patients studied (44.1%). An increased CRP was found in 46 of the 108 patients (42.5%). Seventy-nine percent of the patients (161/204) were on NSAIDs, 17 (8.3%) on methotrexate, 14 (6.8%) on corticoids, 13 (6.3%) on sulphasalazine and 1 (0.49%) on cyclosporin A. Ninety-one patients (44.6%) had active disease at the time of the study.

Abdominal scintigraphy demonstrated gut inflammation in 104 patients (50.9%). The affected sites were: the descending colon in 55 patients (26.9%), the ascending colon in 33 (16.1%), the rectosigmoid in 25 (12.2%), the transverse colon in 18 (8.8%) and the terminal ileum in 17 (8.3%). Twenty-two patients were given a score of 1 (21.1%), 26 were given a score of 2 (25%), 33 were given a score of 3 (31.7%) and 23 were given a score of 4 (22.1%).

Control group

As a control group we studied 54 patients who did not fulfil the criteria of Sp. These patients had been taking NSAIDs for more than 3 months. Chronic low back pain was diagnosed in 19 patients, rheumatoid arthritis in 17, juvenile chronic arthritis in 3, connective tissue disease in 3, septic arthritis in 3, hip or knee replacement in 6, gout arthritis in 1, hepatitis B virus arthritis in 1 and Leriche's syndrome in 1. Abdominal scintigraphy was positive in six patients (2.9%). Gut inflammation was located at the descending colon in four cases and at the ascending colon in two. One patient had septic arthritis due to an intra-abdominal abscess and one patient with low back pain suffered from diverticulitis.

The influence of NSAIDs on abdominal scintigraphy

Treatment with NSAIDs had no influence on the scintigraphic findings, and the rate of "false-positives" was not significant. Patients with a diagnosis of Sp had a significantly higher rate of silent gut inflammation (104/204, 50.9%) than the control group treated with NSAIDs (6/54, 2.9%) (χ^2=27.75; P<0.001; OR=8.32; 95% CI=3.23–22.67).

Clinical associations of positive abdominal scintigraphy in patients with Sp

Abdominal scintigraphy was positive in 53% of the patients diagnosed with undifferentiated Sp, a frequency not significantly different from that in the other diagnostic groups evaluated (Table 1). Furthermore, no statistically significant relation was found with any of the epidemiological parameters studied (Table 2). The presence of radiological findings (sacro-iliitis, syndesmophytes, peripheral joint erosions) and HLA-B27 positivity did not correlate with the percentage of positive scintigraphy studies. There was, however, a relationship between positive scintigraphy and a CRP of >0.5 (though it is to be noted that CRP was studied in only 108 patients) (Table 3).

Clinical activity, as previously defined, was only studied in 141 patients. A statistically significant relationship was noted between clinical activity and silent gut inflammation, demonstrated by abdominal scintigraphy. Abdominal scintigraphy was positive in practically all the patients showing clinical activity. Furthermore, this relationship was present in all of the diagnostic groups (Table 4).

The location of intestinal injuries in patients with Sp was also studied. Injuries were most commonly located in the ascending and descending colon but the differences compared with other sites were not statistically significant. Comparing the individual diagnostic groups, it was found that the terminal ileum was more commonly affected in patients with reactive arthritis or Reiter's syn-

Table 1. Frequency of positive scintigraphy in different spondyloarthropathies

	No.	Positive scintigraphy	%
Ankylosing spondylitis	105	55	43.5
Reiter's syndrome/reactive arthritis	19	9	38.4
Psoriatic arthritis	26	12	38.0
Undifferentiated spondylarthropathy	54	28	53.3

Table 2. Epidemiological data and articular manifestations in patients with positive and negative abdominal scintigraphy

	Positive scintigraphy (n=104)		Negative scintigraphy (n=100)	
	Mean	2 SD	Mean	2 SD
Age at disease onset (years)	36.78	12.78	37.17	12.83
Disease duration (years)	9.21	9.05	9.18	8.48
	No.	%	No.	%
Sex (male)	63	60.57	62	62
Family history of Sp or psoriasis	33	31.73	37	37
Oligo-arthritis	36	34.61	46	46
Polyarthritis	13	12.5	13	13
Mono-arthritis	5	4.807	4	4
Enthesitis	53	50.96	56	56

Table 3. HLA-B27 positivity, CRP level, radiological findings and disease activity in patients with positive and negative abdominal scintigraphy

	Positive scintigraphy (n=64)		Negative scintigraphy (n=77)	
	No.	%	No.	%
HLA-B27 positivity	41/62	66.1	45/70	64.3
CRP >0.5*	34/55	61.8	17/53	32.0
Sacro-iliitis (with or without AS criteria)	41	64.1	49	63.6
Syndesmophytes	7	10.9	12	15.6
Peripheral joint erosion	13	20.3	23	29.9
Active disease**	55	85.9	8	10.3

AS, Ankylosing spondylitis
*χ^2=9.4; P<0.005; OR=3.4; 95% CI=1.5–7.4
**χ^2=80.7; P<0.0001; OR=52.7; 95% CI=19–145.6

Table 4. Relationships between active disease and positive scintigraphy in the different diagnostic groups

	No.	Absence/presence of active disease	No.	Positive scintigraphy	P<	OR	95% CI
Ankylosing spondylitis	62	AD	26	22 (84.6%)	0.0005	34.1	8.2–141.6
		No AD	36	5 (13.9%)			
Reiter's syndrome/reactive arthritis	13	AD	5	5 (100%)	0.001	187	10.5–3,152.3
		No AD	8	0			
Psoriatic arthritis	21	AD	6	5 (83.3%)	0.014	20	1.6–241.7
		No AD	15	3 (20%)			
Undifferentiated spondylarthropathy	45	AD	26	23 (88.4%)	0.0001	138	13.2–1,440
		No AD	19	1 (5.2%)			

AD, Active disease; No AD, no clinical activity

drome than in those with psoriatic arthritis (5/19 vs 0/26; P<0.001; OR=2.59; 95% CI=1.6–4.18).

With regard to intestinal uptake, we found it to be higher among patients with undifferentiated Sp than in the other diagnostic groups.

Discussion

Many clinical observations indicate that the gut plays an important role in the development of Sp. Some gut infections can produce reactive arthritis, and gut inflammation is observed in patients with post-venereal arthritis. There is also an increased prevalence of IBD in families of patients with post-venereal arthritis or ankylosing spondylitis. Cross-reactions between HLA-B27 and some components of intestinal bacteria have been demonstrated [10]. Sulphasalazine has been given for years as a treatment for ulcerative colitis and colonic Crohn's disease, and more recently it has been used for rheumatoid arthritis and Sp [11, 12]. Finally, the ileocolonoscopic evaluation of the large intestine has demonstrated subclinical inflammation in Sp patients [13, 14].

Ileocolonoscopy and biopsies were performed in Sp patients without a background of IBD by Mielants et al. [2], who found acute gut lesions in 25% of patients and chronic gut lesions in 34%. They correlated these microscopic alterations with various clinical, radiological, biological and genetic parameters. Chronic lesions were related to a family history of Crohn's disease and Sp, especially in those patients with ankylosing spondylitis. Acute lesions were related to undifferentiated Sp and reactive arthritis.

The location of these gut lesions is different in Sp patients without IBD and in patients with ulcerative colitis or Crohn's disease. Many authors have corroborated the presence of silent gut inflammation in reactive arthritis, undifferentiated Sp and ankylosing spondylitis by means of ileocolonoscopy [4, 15, 16, 17, 18, 19, 20]. In those studies, out of 500 patients, 168 (33.6%) had macroscopic lesions and 271 (54.2%) had microscopic lesions. Similar lesions have been described in 26% of patients with psoriatic arthritis [21]. These lesions are not related to intake of NSAIDs [18]. In most cases, the healing of the histological gut lesions occurs in parallel with remission of the gut inflammation [22, 23].

Ileocolonoscopy is an invasive process that is not well accepted by the patient in the absence of symptoms. Radio-isotope studies are a good alternative to colonoscopy. Abdominal scintigraphy using ^{99m}Tc-HMPAO-labelled leucocytes is useful to evaluate the extent and activity of the inflammation in ulcerative colitis and Crohn's disease [24, 25, 26]. Our study confirms the findings of previous investigations [5, 6] in that the presence of silent gut in-

flammation was revealed by abdominal scintigraphy in a large number of patients [104 of the 204 Sp patients (50.9%)]. These results agree with those obtained by histological techniques. The epidemiological, clinical and radiological characteristics of our patients were also similar to those of patients in previous studies [15, 16, 17, 18, 19]. Tracer uptake on abdominal scintigraphy is different to that in patients with ulcerative colitis or Crohn's disease [5]. This uptake is not dependent on NSAID intake.

Gut inflammation in Sp patients occurs mainly in the ascending and descending colon, although any other site may be affected. Inflammation of the small intestine and the rectosigmoid is infrequent. This picture is different from that in IBD patients. The presence of silent gut inflammation in patients with Sp was not related to the parameters studied, with the exception of disease activity and an increased CRP. The relationship that we found between gut inflammation and the activity of the illness is similar to that described in histological studies [15, 16, 17, 18, 19], and holds true for all Sp patient groups.

It is possible that the gut inflammation found in many of these patients with Sp is not related to subclinical IBD. Transgenic animal studies expressing HLA-B27 show the pathogenic relationship between the germs, gut lesions and arthritis in the Sp. Transgenic HLA-B2705 mice develop a multisystemic illness with gut and joint inflammation [27]. These problems are not related to any bacteria, but if these mice are bred in a sterile environment they do not develop gut and joint inflammation [3]. This model suggests that the initiating events of the disease take place in the gastrointestinal tract, especially in the colon. The intestinal lesions show a predominantly mononuclear cell infiltrate in the lamina propria [27], similar to that found by ileocolonoscopy in human Sp [2]. Recently we found similar lesions in patients with Sp and positive abdominal scintigraphy [7, 28]. The gut inflammation probably causes an increase in its permeability, and thus stimulates the immune system. An increase in gut permeability in patients with Sp has been demonstrated [25, 29], and this increased permeability correlated only with histological changes of chronic gut inflammation [29]. Stodell et al. [30] found an increase of IgG-containing cells in the lamina propria of the rectal mucosa in patients with ankylosing spondylitis, suggesting a local immune response in the bowel. Antigens in the gastrointestinal lumen may pass through the gut mucosa into the circulation, and it has been suggested that there is transport of the antigen and the cells of these antigens to the joints [31, 32]. It has been postulated that Gram-negative enteric bacteria crossing the gut wall stimulate antigen-antibody reactions with the HLA-B27 structure [33] or with HLA-B27-associated structures on cells of the target organs by molecular mimicry [34], or that they may alter the peptide sequence on HLA-B27 molecules on human monocytes [35].

The gut could play an important pathogenetic role in different forms of Sp, permitting exogenous factors to enter the circulation [15]. It is possible, as B27 transgenic rat models suggest, that the gut inflammation is the first event in the development of Sp. Independently of whether the diagnosis is ankylosing spondylitis or another form of Sp, abdominal scintigraphy using ^{99m}Tc-HMPAO-labelled leucocytes is of value to detect the silent gut inflammation in Sp patients. The relation between the histological findings or the gut inflammation detected by scintigraphy and the activity of the illness shows that the subclinical inflammation can be important in the maintenance or the reactivation of joint inflammation in Sp patients. Because of the relationship between the uptake on scintigraphy and the activity of the illness from a clinical point of view, scintigraphy could be a useful tool for evaluating the therapeutic response [36].

Acknowledgements. The authors thank Dr. M.L. Gonzalez, Dr. P. Dominguez Montero, Dr. A. Bittini Copano and M.L. Martinez Puello for providing helpful and insightful comments.

This work was supported by a grant from the Fondo de Investigaciones Sanitarias (96/0652 FIS) and Consejeria de Sanidad de la Junta de Comunidades de Castilla-La Mancha (96323).

References

1. Dougados M, Van der Linden S, Juhlin R, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991; 34: 1218–1227.
2. Mielants H, Veys EM, Goemaere S, Goethals K, Cuvelier C, De Vos M. Gut inflammation in the spondyloarthropathies: clinical, radiologic, biologic and genetic features in relation to the type of histology. A prospective study. *J Rheumatol* 1991; 18: 1542–1551.
3. Taurog JD, Richardson JA, Croft JT, Simmons W, Zhou M, Fernández-Sueiro JL, Balasch E, Hammer R. The germfree state prevents development of gut and joint inflammatory disease in HLA-B 27 transgenic rats. *J Exp Med* 1994; 180: 2359–2364.
4. De Keyser F, Elewaut D, De Vos M, et al. Bowel inflammation and the spondyloarthropathies *Rheum Dis Clin North Am* 1998; 24: 785–813.
5. Alonso JC, López-Longo FJ, Lampreave JL, González CM, González M, Almoguera I, Carreño L. Different abdominal scintigraphy pattern in patients with ulcerative colitis, Crohn's disease and seronegative spondylarthropathies. *Br J Rheumatol* 1995; 34: 946–950.
6. Alonso JC, López-Longo FJ, Lampreave JL, González CM, Vegazo O, Carreño L, Almoguera I. Abdominal scintigraphy using ^{99m}Tc-HMPAO-labelled leucocytes in patients with seronegative spondylarthropathies without clinical evidence of inflammatory bowel disease. *Eur J Nucl Med* 1996; 23: 243–246.
7. El Maghraoui A, Dougados M, Freneaux E, Chaussade S, Amor B, Breban M. Concordance between abdominal scintigraphy using technetium-99m hexamethylpropylene amine oxime-labelled leucocytes and ileocolonoscopy in patients with spondyloarthropathies and without clinical evidence of inflammatory bowel disease. *Rheumatology* 1999; 38: 543–546.

8. Vorne M, Soini I, Lantto T, et al. Technetium-99m HMPAO-labelled leukocytes in detection of inflammatory lesions: comparison with gallium-67 citrate. *J Nucl Med* 1989; 30: 1332–1336.
9. Blasco R, Lasa D, Mata F, Piera C, Ramírez-Arellano I, Roca M. Manual de procedimientos radiofarmacéuticos "Marcaje de leucocitos con HMPAO". *Rev Esp Med Nucl* 1996; 6: 438–440.
10. Taurog JD. Seronegative spondylarthropathies A. Epidemiology, pathology and pathogenesis. In: Klippel JH, ed. *Primer on the rheumatic diseases.* Atlanta: Arthritis Foundation; 1997: 180–183.
11. Mielants H, Veys EM, Joos R. Sulphasalazine in the treatment of enterogenic reactive synovitis and ankylosing spondylitis with peripheral arthritis. *Clin Rheumatol* 1986; 5: 80–83.
12. Fraser SM, Sturrock RD. Evaluation of sulphasalazine in ankylosing spondylitis. *Br J Rheumatol* 1990; 29: 37–39.
13. Mielants H, Veys EM, Cuvelier C, et al. HLA-B 27 related arthritis and bowel inflammation. II. Ileocolonoscopy and bowel histology in patients with HLA-B 27 related arthritis. *J Rheumatol* 1985; 12: 294–298.
14. Smith MD, Gibson RA, Brooks PM. Abnormal bowel permeability in ankylosing spondylitis and rheumatoid arthritis. *J Rheumatol* 1985; 12: 299–301.
15. Mielants H, Veys EM, Cuvelier C, De Vos M. Course of gut inflammation in spondylarthropathies and therapeutic consequences. *Bailliere's Clin Rheumatol* 1996; 10: 147–164.
16. Grillet B, De Clerck L, Dequeker J, et al. Systematic ileocolonoscopy and bowel biopsy in spondylarthropathy. *Br J Rheumatol* 1987; 26: 338–340.
17. Simenon G, Van Gossum A, Adler M, Rijckaert F, Appelboom T. Macroscopic and microscopic gut lesions in seronegative spondylarthropathies. *J Rheumatol* 1990; 17: 491–494.
18. Lee YH, Ji JD, Kim JS, et al. Ileocolonoscopic and histological studies in Korean patients with ankylosing spondylitis. *Scand J Rheumatol* 1997; 26: 473–476.
19. Leirisalo-Repo M, Turunen U, Stenman S, Helenius P, Seppälä K. High frequency of silent inflammatory bowel disease in spondylarthropathy. *Arthritis Rheum* 1994; 37: 23–31.
20. Altomonte L, Zoli A, Veneziani A, et al. Clinically silent gut lesions in undifferentiated spondyloarthropathies. *Arthritis Rheum* 1994; 13: 565–570.
21. Schatteman L, Mielants H, Veys EM, et al. Gut inflammation in psoriatic arthritis: a prospective ileocolonoscopic study. *J Rheumatol* 1995; 22: 680–683.
22. Mielants H, Veys EM, De Vos M, et al. The evolution of spondylarthropathies in relation to gut histology. I. Prospective study of the clinical spondylarthropathy. *J Rheumatol* 1995; 22: 2266–2272.
23. Mielants H, Veys EM, Joos R, et al. Repeat ileocolonoscopy in reactive arthritis. *J Rheumatol* 1987; 14: 456–458.
24. Schemichen C, Schoelmerich J. Specificity of Tc-99m-HMPAO-labelled leukocyte uptake in the large bowel as an indicator of inflammatory bowel disease. *Nuklearmedizin* 1987; 24: 370–374.
25. Lantto E, Jàrvi K, Krekelá I, et al. Technetium-99m hexamethyl propylene amine oxime leukocytes in the assessment of disease activity in inflammatory bowel disease. *Eur J Nucl Med* 1992; 19: 14–18.
26. Wendling D, Bidet A, Guidet M. Intestinal permeability in ankylosing spondylitis. *J Rheumatol* 1990; 17: 114.
27. Hammar RE, Maika S, Richardson JA, Tang J, Taurog JD. Spontaneous inflammatory disease in transgenic rats expressing HLA-B 27 and human beta2-m: an animal model of HLA-B 27-associated human disorders. *Cell* 1990; 63: 1099–1112.
28. Monteagudo I, López-Longo FJ, Montilla CA, González CM, Moreno M, Menchén P, Lara V, Carreño L. Positive abdominal scintigraphy in patients with spondyloarthropathy: what is the morphological significance? [abstract]. 62nd National Scientific Meeting, American College of Rheumatology, November 8–12, 1998, San Diego. *Arthritis Rheum* 1998; 41 (Suppl): S110.
29. Mielants H, De Vos M, Goemaere S, Schelstraete K, Cuvelier C, Goethals K, Maertens M, Ackerman C, Veys EM. Intestinal mucosal permeability in inflammatory rheumatic diseases. 2. Role of disease. *J Rheumatol* 1991; 18: 394–400.
30. Stodell MA, Butler RS, Zemelman VA, Henry K, Brewerton D. Increased numbers of IgG-containing cells in rectal lamina propria of patients with ankylosing spondylitis. *Ann Rheum Dis* 1985; 43: 172–176.
31. Salmi M, Andrew DP, Butcher EC, Jalkanen S. Dual binding capacity of mucosal immunoblasts to mucosal and synovial endothelium in humans: dissection of the molecular mechanisms. *J Exp Med* 1995; 181: 137–149.
32. Segal AH: Anatomic predilection of the spondyloarthropathies: a case of the nerves? *J Rheumatol* 1996; 23: 491–494.
33. Seager K, Bashir HV, Geczy AF. Evidence for a specific B 27-associated cell surface marker in lymphocytes of patients with ankylosing spondylitis. *Nature* 1979; 277: 68–70.
34. Williams KM, Raybourne RB. Demonstration of cross-reactivity between bacterial antigens and class I human leukocyte antigens by using monoclonal antibodies to *Shigella flexneri*. *Infect Immun* 1990; 58: 1774–1781.
35. Wuorela M, Jalkanen S, Kirveskari J, Laitio P, Granfors K. *Yersinia enterocolitica* serotype O:3 alters the expression of serologic HLA-B27 epitopes on human monocytes. *Infect Immun* 1997; 65: 2060–2066.
36. González CM, López-Longo FJ, Monteagudo I, González ML, Bascones M, Moreno M, Montilla CA, Carreño L. Seronegative spondyloarthropathies and subclinical gut inflammation: clinical course and abdominal scintigraphic changes in treated patients [abstract]. 62nd National Scientific Meeting, American College of Rheumatology, November 8–12, 1998, San Diego. *Arthritis Rheum* 1998; 41 (Suppl): S110.