

Elsevier Editorial System(tm) for Joint Bone Spine
Manuscript Draft

Manuscript Number:

Title: The DESIR cohort: A ten-year follow-up of early inflammatory back pain in France: Study design and baseline characteristics of the 708 recruited patients.

Article Type: Original article

Keywords: Spondyloarthritis; ankylosing spondylitis; cohort

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Manuscript Region of Origin: FRANCE

Abstract: Objectives: The French Society of Rheumatology has initiated a large national multicenter, longitudinal, prospective follow-up of patients presenting with early inflammatory back pain in order to set up a database to facilitate several investigations on diagnosis, prognosis, epidemiology, pathogenesis and medico-economics in the field of early inflammatory back pain and spondyloarthritis. Methods: Patients were recruited if they had inflammatory back pain of more than 3 months and less than 3 years. Patients will be followed every 6 months during the first 2 years then every year during at least 5 years. Apart from information collected on a Case Report Form (demographics, disease activity, severity, co-morbidities, socio-economics, treatments, radiological and MRI evaluation of the spine and the pelvis according to the local investigators, and for some centers bone densitometry and ultrasonography of entheses), the digital X-rays and MRI of the spine and pelvis are stored using a specific software (Carestream) and the biological samples (DNA, RNA, sera, urines) are centralized at the Biological Resources Center (Bichat Hospital).

Results: The recruitment period of the 708 patients (mean age: 34±9 years, female 54%, HLA-B27 positive: 57%) in the 25 centers was 26 months (from December 2007 to April 2010). The modified New York criteria, Amor criteria, ESSG criteria and axial ASAS criteria were fulfilled by 26%, 77%, 76% and 67% of the patients at entry respectively. A history or current symptoms suggestive of peripheral arthritis, acute anterior uveitis and inflammatory bowel disease were observed in 21%, 9% and 4% of the patients respectively. The disease was active (BASDAI: 45±20) despite an NSAID intake in 66% of the patients.

Conclusion: This large cohort should facilitate the conduct of researches in different areas (clinical, medico-economics, translational) in order to improve our knowledge on the pathogenesis and natural history of axial spondyloarthritis.

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Abstract

Objectives: The French Society of Rheumatology has initiated a large national multicenter, longitudinal, prospective follow-up of patients presenting with early inflammatory back pain in order to set up a database to facilitate several investigations on diagnosis, prognosis, epidemiology, pathogenesis and medico-economics in the field of early inflammatory back pain and spondyloarthritis.

Methods: Patients were recruited if they had inflammatory back pain of more than 3 months and less than 3 years. Patients will be followed every 6 months during the first 2 years then every year during at least 5 years. Apart from information collected on a Case Report Form (demographics, disease activity, severity, co-morbidities, socio-economics, treatments, radiological and MRI evaluation of the spine and the pelvis according to the local investigators, and for some centers bone densitometry and ultrasonography of entheses), the digital X-rays and MRI of the spine and pelvis are stored using a specific software (Carestream) and the biological samples (DNA, RNA, sera, urines) are centralized at the Biological Resources Center (Bichat Hospital).

Results: The recruitment period of the 708 patients (mean age: 34 ± 9 years, female 54%, HLA-B27 positive: 57%) in the 25 centers was 26 months (from December 2007 to April 2010). The modified New York criteria, Amor criteria, ESSG criteria and axial ASAS criteria were fulfilled by 26%, 77%, 76% and 67% of the patients at entry respectively. A history or current symptoms suggestive of peripheral arthritis, acute anterior uveitis and inflammatory bowel disease were observed in 21%, 9% and 4% of the patients respectively. The disease was active (BASDAI: 45 ± 20) despite an NSAID intake in 66% of the patients.

Conclusion: This large cohort should facilitate the conduct of researches in different areas (clinical, medico-economics, translational) in order to improve our knowledge on the pathogenesis and natural history of axial spondyloarthritis.

1. Introduction

The group of diseases collectively now labeled spondyloarthritis consists of several disorders: psoriatic arthritis, reactive arthritis, arthritis related to inflammatory bowel disease, a subgroup of juvenile chronic arthritis and ankylosing spondylitis, with the last mentioned being the prototype of spondyloarthritis [1-3]. The different clinical manifestations observed in these disorders include spinal (axial) manifestations, peripheral arthritis, enthesitis and extra-articular features such as uveitis, psoriasis and inflammatory bowel disease. The clinical argument in favor of this concept is the fact that such disorders may occur simultaneously or sequentially in a same patient or in a member of his/her family. In addition, some of the clinical characteristics of these diseases such as eye involvement and enthesitis are similar whatever the diagnosis [1,2]. An experimental argument in favor of this concept is the fact that HLA-B27 transgenic rats develop the different clinical manifestations observed in humans with spondyloarthritis [4].

The axial symptoms are the most frequent and predominant at an early stage of the disease. Spondyloarthritis is usually occurring in young adults and might have a dramatic impact on the quality of life of patients. However, the natural history of spondyloarthritis seems be heterogeneous with several forms from mild to severe disease. The current unresolved questions in the field of spondyloarthritis can be summarized in the following sub-categories:

- *Diagnosis*: sets of criteria [5-7] enabling the recognition of the disease at an early stage have been recently proposed [8] but require additional validation in a different setting.
- *Prognosis*: the natural history of axial spondyloarthritis is not well known [9-11]. The recognition of prognostic markers will facilitate the therapeutical decision at an early stage of the disease in particular the indication of drugs such as the TNF blockers which are costly but dramatically efficient [12,13]. Such markers could be either a specific phenotype observed at an early stage of the disease or a biological marker such as acute phase reactants, cytokines, DNA or RNA specific expressions.
- *Public health services*: few data are available in France about quality of life and socio-economic consequences of spondyloarthritis [14,16].

These questions would be better addressed by obtaining periodic and prolonged follow-up over several years of patients presenting with early inflammatory back pain. To our knowledge, the first systematic prospective follow-up of patients with axial spondyloarthritis is the OASIS (Outcome in Ankylosing Spondylitis International Study) which included

1 consecutive patients seen in 3 European departments of rheumatology with a mean disease
2 duration of 12 years [16]. Another similar cohort (*e.g.* including patients at various duration
3 stage of their disease) is also ongoing in Spain under the acronym of Regisponder [17]. In
4 fact, only 2 recent cohorts are focused on patients seen at an early stage of the disease *e.g.* in
5 Germany, the GESPIC (German Spondyloarthritis Inception Cohort) cohort [18] and in the
6 Netherlands the EsPac (Early Spondyloarthropathy Clinic) [19]. More recently, the French
7 Society of Rheumatology initiated a large national multicenter cohort, the so-called “DESIR
8 cohort study” to facilitate investigations on diagnostic and prognostic markers but also
9 aetiologic, pathogenic and socio-economic factors among patients with early inflammatory
10 back pain suggestive of axial spondyloarthritis. DESIR is a French acronym for “DEvenir des
11 Spondyloarthropathies Indifférenciées Récentes”, “Outcome of recent undifferentiated
12 spondyloarthritis”.

25 **2. Methods**

27 **1. Study design**

29 This is a longitudinal prospective cohort study in adults aged over 18 and less than
30 50 years from 25 regional centers in France. This study is fulfilling the current Good Clinical
31 Practice Guidelines and has obtained the approval of the appropriate ethical committee.
32 Participants at the study gave their written informed consent. A website containing the
33 detailed description of the centers, the organization of the cohort but also the full detailed
34 protocol and CRF is accessible at the following address: www.lacohortedesir.fr

42 **2. Sample size**

44 The sample size of the study has been calculated based on the primary objective *e.g.* the
45 predictive validity of sacroiliac MRI evaluation. In other words, this calculation has been
46 made on the probability to detect structural changes of the sacroiliac joints based on a pelvic
47 X-rays after a follow-up of 5 years based on the presence of MRI signs of inflammation of the
48 sacroiliac joints at baseline (*e.g.* “positive” MRI). According to the data available at the time
49 of the elaboration of the protocol it was anticipated that 30 to 50% of the recruited patients
50 will have an “abnormal” MRI. It was also anticipated that after a 5 years follow-up period, 70
51 to 90% of the patients with a “positive” baseline MRI will have structural changes of the
52 sacroiliac joints observed on pelvic X-rays. The sample size calculation was made on this
53 hypothesis and on a relative risk between 2 and 3 to observe structural changes on pelvic X-

1 rays at year 5 with the regard to the MRI findings at baseline (*e.g.* “positive” *versus*
2 “negative”) with a 90% statistical power. Based on these different calculations (see the
3 protocol for detailed explanation [section 2.a.]) and also on the estimated 15 to 20% lost of
4 follow-up, the sample size was estimated between 685 and 785. The final decision was to
5 recruit 700 patients.
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10 **3. Inclusion criteria**

- 11 1. Patients aged over 18 and under 50 years
- 12 2. Inflammatory back pain (buttock, lumbar or thoracic spine) fulfilling either the Calin or
13 Berlin criteria [20,21]
- 14 3. Symptom duration more than 3 months and less than 3 years
- 15 4. Symptoms suggestive of spondyloarthritis according to the local investigator’s assessment
16 (*e.g.* score ≥ 5 on a 0 to 10 numerical rating scale in which 0 = no suggestive and 10 = very
17 suggestive of spondyloarthritis)
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25 **4. Non-inclusion criteria**

- 26 1. Other spinal disease clearly defined (*e.g.* discarthrosis)
- 27 2. History of any biotherapy
- 28 3. Corticosteroid intake was permitted only in case of a dose lower than 10 mg prednisone
29 per day and stable for at least 4 weeks prior baseline
- 30 4. History or current disorders which might interfere with the validity of the informed
31 consent and/or prevent an optimal compliance of the patient to the cohort (*e.g.* alcoholism,
32 psychological disorders)
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43 **5. Patient recruitment**

44 Centers (25) were selected based on the experience of investigators in conducting multi-
45 center controlled trials, longitudinal epidemiological studies and had to fulfill pre-defined
46 quality standards (see Annex II of the protocol). Recruitment was performed in close
47 connection with local community rheumatologists. Each center acted as an observational
48 center and did not interfere with patient treatment. The management of the patients was under
49 the supervision of his/her rheumatologist.
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58 **6. Patient follow-up**

1 In order to improve the compliance of the patients to the study protocol and, in particular,
2 to the planned visits at the regional center, several initiatives were performed such as a
3 birthday card sent by the organizing committee, a bi-annual letter to the patients and a bi-
4 annual letter to the rheumatologists who have referred at least one patient in the cohort, a
5 written recall for each individual patient one week before each planned visit, ...
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10 **7. Collected parameters**

11 *1. Clinical parameters*

12 These parameters are collected on a Case Record Form, demographics at baseline only
13 and at each visit the following:
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- 15 - the physical examination (*e.g.* height, weight, blood pressure, modified Schober's test,
16 chest expansion, occiput-to-wall distance, tragus-to-wall distance, finger-to-floor distance,
17 lateral spinal flexion, inter-malleolar distance, cervical spine rotation , BASMI [22];
- 18 - ongoing treatments with a particular focus on the treatment required by the spinal disease
19 (*e.g.* analgesics, NSAIDs, DMARDs including biologics, physiotherapy); the NSAID
20 intake collection is done in accordance with the ASAS recommendations [23];
- 21 - co-morbidities with a specific check-list including in particular cardiovascular and
22 malignant diseases;
- 23 - questionnaires self assessed by the patient (*e.g.* BAS-G [24], BASDAI [25], BASFI [26],
24 HAQ-AS [27], SF36 [28], Euro-QoL [29], health resource use and impact of work limited
25 to absenteeism, disability pension and early retirement due to the disease);
- 26 - overall assessment of the investigators concerning the probability of diagnosis of
27 spondyloarthritis using a 0-10 Numerical Rating Scale;
- 28 - other main clinical features of spondyloarthritis (*e.g.* acute anterior uveitis, psoriasis,
29 inflammatory bowel disease, enthesitis assessed by the Maastricht Ankylosing
30 Spondylitis Enthesitis Score [30], peripheral articular involvement assessed by the 28 joint
31 count for synovitis and the 53 joint count for tenderness).

32 *2. Biological parameters*

33 a) Local evaluation

34 Erythrocyte Sedimentation Rate and C Reactive Protein are collected annually enabling
35 the calculation of ASDAS [31,32]
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37 Cholesterol (HDL, LDL) and blood count are collected bi-annually during the first 2 years
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39 b) Central evaluation

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1 The central biological samples are stored in the Biological Resources Center at Bichat
2 Hospital (accreditation AFNOR #34457)

3 Such evaluations include:

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5 - DNA sample at the second visit (month 6 of the study)
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7 - RNA sample at baseline
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9 - Serum at the following visits: baseline, month 6, 12, 24 and 60
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11 - Urine at the following visits: baseline, month 24 and month 60
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13 14 3. *Plain X-rays evaluation*

15 a) Data collected

16 Plain X-rays included the following views:

- 17
18 - cervical spine lateral
19
20 - thoracic spine lateral
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22 - lumbar spine antero-posterior and lateral
23
24 - pelvis antero-posterior
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26 with a specific procedure for their collection (see annex 2.b. of the protocol). These plain
27 X-rays are collected systematically at baseline and at month 12, 24 and 60 of the study
28

29 b) Evaluation

30 The evaluation is performed at 2 levels

- 31
32 - the local level by either the radiologist or the rheumatologist filling the forms of the CRF
33 permitting to calculate the mSASSS [33] and the BASRI [34];
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35 - the central level thanks to a storage of all the CDs of such X-rays evaluation on a specific
36 software (Carestream). This storage will permit subsequent evaluations by different
37 researchers.
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45 4. *MRI evaluation*

46 a) Data collected

47 A MRI of the spine and the pelvis is collected at baseline in all patients. For the patients
48 recruited in the centers of Assistance Publique - Hôpitaux de Paris (7 centers) a systematic
49 MRI is also collected at month 12, 24 and 60 of the study.
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51 b) Evaluation

52 A similar methodology as for the plain X-rays has been applied. Concerning the
53 evaluation at the regional/local center level, the information collected is only binary (presence
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2 of inflammatory lesions yes/no, presence of structural changes yes/no) at the spinal and
3 sacroiliac level according to the ASAS recommendations [35].
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5 *5. Other collected parameters*

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7 For the centers willing to participate and having the expertise for that, two other
8 investigations were performed:
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- 10 - bone densitometry (12 centers)
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12 - ultrasonography of bilateral insertion of the extensor common on lateral epicondyle,
13 patellar ligament insertion of the apex of patella and on tibial tuberosity and the Achilles
14 tendon insertion on the calcaneus (14 centers)
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20 **8. Databases**

21 Three different databases have been constituted:
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- 23 1. The clinical database: at each visit, the local investigator has to send a copy of all the
24 pages of the CRF corresponding to this visit to a CRO (ClinInfo) which performs a
25 double data entry. The database has been elaborated by the Department of Statistics in
26 Nîmes which is also in charge of the monitoring of the patients in collaboration with
27 the Clinical Research Unit of Paris Centre.
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29 2. The biological database permits the storage of the biological samples according to the
30 Good Laboratory Practice Guidelines in Bichat Hospital.
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32 3. The imaging database permits the storage of all plain X-rays and MRI films in the
33 Clinical Research Unit (Cochin Hospital).
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42 **9. Monitoring**

43 The clinical Research Unit of Paris Centre (Assistance Publique - Hôpitaux de Paris) is in
44 charge of the monitoring of the study *via* Clinical Research Assistants in charge of
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- 46 - opening of the different centers
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48 - annual visit on sites of the different centers
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50 - management of the potential queries
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54 **10. Organization and Committees**

55 *Steering committee:* the steering committee is in charge of organizational, administrative
56 and financial coordination of the cohort.
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Scientific committee: the scientific committee includes the steering committee members, and also national and international experts in the field of spondyloarthritis; it is in charge of evaluating and validating scientific projects to be performed using the cohort databases.

A RFP (Request For Proposals) is sent bi-annually to all the steering and scientific committee members and also to the investigators using a specific form. Each application is reviewed by internal and external reviewers.

This procedure is restricted to the participants at the cohort for the 2 years following the lock of the database for a specific visit. For example, in June 2010, the database of the baseline visit has been locked. Projects proposed by researchers not involved in the DESIR cohort will be acceptable after June 2012.

Funding Sources: this study is conducted as a PHRC (Programme Hospitalier de Recherche Clinique) with Assistance Publique – Hôpitaux de Paris as the sponsor. This study is conducted under the umbrella of the French Society of Rheumatology which is also financially supporting this cohort. An unrestricted grant from Pfizer has been allocated for the first 5 years.

3. Results

1. Patients inclusion

A total of 708 patients with early inflammatory back pain were included between October 2007 and April 2010. All the centers were active and each regional center recruited between 3 and 73 patients (median 28).

2. Patients characteristics

The main characteristics of the patients are summarized in Table I and the activity and severity parameters of the disease are summarized in Table II with regard to the different available sets of criteria.

4. Discussion

This manuscript is summarizing the methodology and the baseline characteristics of the 708 patients with early inflammatory back pain.

1 The baseline characteristics of the patients and in particular the percentage of patients with
2 MRI findings suggestive of inflammatory lesion of the sacroiliac joints (*e.g.* 33%) is very
3 close to the anticipated one (between 30 to 50%).
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5 Moreover, the relatively high percentage of patients fulfilling at entry the sets of criteria
6 for spondyloarthritis confirms the validity of this cohort for which one of the main objective is
7 to evaluate the natural history of axial spondyloarthritis.
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10 As observed in other cohorts focusing on patients with early inflammatory back
11 pain [18,19], the sex ratio is well balanced with, in the DESIR cohort, 54% of women in
12 contrast with the traditional male predominance in ankylosing spondylitis. The longitudinal
13 follow-up of the patients recruited in the DESIR cohort will permit to see whether the natural
14 history is gender related or not.
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19 The relatively high percentage of patients with history or current symptoms (in addition to
20 the axial symptoms) suggestive of spondyloarthritis is remarkable (see Table I). These
21 findings confirm the interest to include these parameters (*e.g.* usually called Spondyloarthritis
22 Clinical features) in the sets of criteria aimed at recognizing patients at an early stage of the
23 disease.
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29 At baseline, despite NSAIDs intake, the disease was active in the majority of the patients
30 with a mean BASDAI of 45 on a 0-100 scale, and over 40 in 60% suggesting that these
31 patients may be or will become very rapidly candidates to TNF blockers. This cohort should
32 permit to evaluate the clinical interest of this therapy in daily practice at an early stage of the
33 disease.
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38 More importantly, the organization of this cohort and, in particular, the quality of the
39 different databases (clinical, biological and radiological) should facilitate the development of
40 multiple research projects in various fields such as diagnosis, prognosis, epidemiology,
41 pathogenesis, management and medico-economy.
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Acknowledgments

The DESIR cohort is conducted under the control of Assistance Publique-Hôpitaux de Paris *via* the Clinical Research Unit Paris-Centre and under the umbrella of the French Society of Rheumatology and INSERM (Institut National de la Santé et de la Recherche Médicale). The database management is performed within the department of epidemiology and biostatistics (Professeur Jean-Pierre Daurès, D.I.M., Nîmes, France). An unrestricted grant from Pfizer Pharmaceuticals was allocated for the first 5 years of the follow-up of the recruited patients. We also wish to thank the different regional participating centers : Pr Maxime Dougados (Paris-Cochin B), Pr André Kahan (Paris-Cochin A), Pr Olivier Meyer (Paris-Bichat), Pr Pierre Bourgeois (Paris-La Pitié-Salpêtrière), Pr Francis Berenbaum (Paris-Saint Antoine), Pr Pascal Claudepierre (Créteil), Pr Maxime Breban (Boulogne Billancourt), Dr Bernadette Saint-Marcoux (Aulnay-sous-Bois), Pr Philippe Goupille (Tours), Pr Jean-Francis Maillefert (Dijon), Dr Xavier Puéchal (Le Mans), Pr Daniel Wendling (Besançon), Pr Bernard Combe (Montpellier), Pr Liana Euller-Ziegler (Nice), Pr Pascal Richette (Paris-Lariboisière), Pr Pierre Lafforgue (Marseille), Dr Patrick Boumier (Amiens), Pr Jean-Michel Ristori (Clermont-Ferrand), Dr Nadia Mehzen (Bordeaux), Pr Damien Loeuille (Nancy), Pr René-Marc Flipo (Lille), Pr Alain Saraux (Brest), Pr Corine Miceli (Le Kremlin-Bicêtre), Pr Alain Cantagrel (Toulouse), Pr Olivier Vittecoq (Rouen). We wish to thank the research nurses, the staff members of the Clinical Research Unit of Paris Centre, the staff members of the Biological Resource Center of Bichat Hospital, the staff members of the Department of statistics of Nîmes and also all the investigators and in particular Jérôme Allain, Emmanuelle Dernis, Salah Ferkal, Clement Prati, Marie-Agnès Timsit, Eric Toussirot for active patients recruitment and monitoring.

Table I: Baseline characteristics (demographics and clinical features of spondyloarthritis) of the 708 recruited patients in the DESIR cohort with regard to the fulfillment of the different sets of spondyloarthritis set of criteria.

Characteristic	Set of criteria*				All patients
	mNY	Amor	ESSG	ASAS	
Number	181	548	549	475	708
Age (year, mean±SD)	31.3±9	33.4±8.6	33.4±8.7	33±8.6	33.8±8.6
Males (%)	58.6	47.3	47.2	50.3	46.2
HLA B27 positive (% patients)	72.4	66.1	58.8	83.2	57.3
Symptoms duration (months, mean±SD)	19±10.1	18.5±11.5	18.7±11.5	18.8±11.6	18.4±11.2
<i>First localization of the clinical symptoms</i>					
- Buttock (% patients)	49.7	41.6	40.4	40	39.6
- Lumbar spine (% patients)	55.8	65	65.8	63	67.1
- Thoracic spine (% patients)	18.2	24.1	22.6	24.6	23.3
- Cervical spine (% patients)	8.3	10.6	10.6	9.7	11.2
<i>Past history or current symptoms of</i>					
- Anterior chest wall pain (% patients)	46.4	47.6	46.8	47.4	44.6
- Peripheral arthritis (% patients)					
o Any including arthralgia	52.5	60.8	61.6	55	56.9
o Synovitis	22.1	25	23.3	21.5	21.3
- Enthesiopathy (% patients)					
o At any site	41.4	55.5	63.2	47.8	49
o Heel pain	33.7	46.7	53.6	38.5	41.5
- Acute anterior uveitis (% patients)	11.1	9.3	9.1	9.7	8.5
- Inflammatory bowel disease (% patients)	7.2	4.9	5.5	4.2	4.2
- Psoriasis (% patients)	14.4	18.6	20	16	15.8
- Investigator's overall assessment**	8.2±1.8	7.3±2.4	7.1±2.6	7.3±2.3	6.8±2.7

*mNY = modified New York Criteria, ESSG = European Spondyloarthritis Study group, ASAS = Axial Assessment in SpondyloArthritis

**overall assessment of the investigators concerning the probability of diagnosis of spondyloarthritis using a 0-10 Numerical Rating Scale

Table II: Baseline characteristics (activity and severity of spondyloarthritis) of the 708 recruited patients in the DESIR cohort with regard to their fulfillment of the different spondyloarthritis sets of criteria.

Characteristic	Set of criteria*				All patients
	mNY	Amor	ESSG	ASAS	
BASG ¹ (last week, mean±SD)	45±26.8	50.7±25.9	50.9±26	48.8±26.4	50.9±25.6
BASDAI ² (mean±SD)	40.1±20.9	44.7±20.3	45.3±20.4	43±20.4	44.7±20
BASDAI ≥40 (% patients)	50.3	60.4	62.1	56.6	60
Abnormal CRP ³ (% patients)	49.2	64.4	65.4	62.7	67.8
CRP (mg/l, mean±SD)	11.4±15.2	8.5±14.8	8.2±14.3	8.5±13.9	7.6±13.7
ASDAS-CRP ⁴ (mean±SD)	3.0±1.3	3.0±1.2	3.0±1.2	3.0±1.2	3.0±1.2
BASFI ⁵ (mean±SD)	28.2±22.3	31.3±22.7	31.5±23.0	29.7±22.4	30.5±22.8
BASMI ⁶ (mean±SD)	2.4±0.9	2.3±0.9	2.3±0.9	2.2±0.9	2.2±0.9
Radiological sacroiliitis ⁷ (% patients)	100	32.3	33	38.1	25.6
MRI abnormalities of the sacroiliac joints ⁸ (% patients)	70.2	36.9	34.4	47.4	31.8
MRI abnormalities of the spine ⁹ (% patients)	34.3	21.5	20.6	25.5	20.2
NSAIDs intake ¹⁰ (% patients)	71.3	70.8	67.2	72	66
ASAS-NSAID score ¹¹ (m±SD)	124.2±108.6	101.9±155.1	110.8±102.9	102.3±158.5	96.7±144.1

¹BASG: Bath Ankylosing Spondylitis Global assessment (0-100)

²BASDAI: Bath Ankylosing Spondylitis Disease Activity Index (0-100)

³Abnormal CRP: CRP above 6 mg/l

⁴AS-DAS Ankylosing Spondylitis – Disease Activity Score

⁵BASFI: Bath Ankylosing Spondylitis Functional Index (0-100)

⁶BASMI: Bath Ankylosing Spondylitis Metrology Index (0-10)

⁷Radiological sacroiliitis: Percentage of patients with an obvious change in at least one sacroiliac joint. The investigator had to quote each sacroiliac joint has normal/doubtful/obvious/fusion evaluated by the local radiologist or rheumatologist

⁸MRI inflammatory lesion of the sacroiliac joints: Percentage of patients with presence of sub-chondral bone edema evaluated by the local radiologist or rheumatologist

⁹MRI inflammatory lesion of the spine: Percentage of patients with presence of lesion of the vertebral corner suggestive of spondyloarthritis evaluated by the local radiologist or rheumatologist

¹⁰NSAID intake: % patients with NSAID intake at baseline

¹¹ASAS-NSAID score: Score evaluated during the last 6 months preceding baseline (n=618) or from the beginning of the symptoms for those who had their first symptoms during the 6 months preceding baseline (n=90)

*mNY = modified New York Criteria, ESSG = European Spondyloarthritis Study Group, ASAS = Axial Assessment in SpondyloArthritis