CLINICAL SCIENCE

Low incidence of vertebral fractures in early spondyloarthritis: 5-year prospective data of the DESIR cohort

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Handling editor Josef S Smolen

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2018-213922).

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Received 11 June 2018
Revised 26 September 2018
Accepted 16 October 2018
Published Online First 2 November 2018

To cite: Sahuguet J, Fechtenbaum J, Molto A, *et al*. *Ann Rheum Dis* 2019;**78**:60–65.

ABSTRACT

Objectives An increased risk of vertebral fractures (VFs) has been reported in spondyloarthritis (SpA). Our hypothesis is that the prevalence of VFs is lower than reported in previous studies, especially in early SpA. This study aimed at assessing the incidence of radiographical VFs over 5 years in early axial SpA.

Methods The DESIR (DEvenir des Spondylarthropathies Indifférenciées Récentes) cohort, which included patients with inflammatory back pain highly suggestive of axial SpA, is the basis of this study. All radiographs of the DESIR cohort had been assessed at a central facility, by one investigator specialised in the field of the diagnosis of VFs according to Genant's method. We assessed the prevalence and incidence of VFs and vertebral deformities at baseline and over 5 years.

Results Five-year X-rays were available for 432 patients (mean age 34.3±8.7 years, 53% women). Diagnosis of VF was doubtful and needed adjudication for 19 patients (4.4%). 13 patients had prevalent VFs (3.0%) which were located at the thoracic spine (12 were grade 1). At 5 years, five patients had an incident VF (1.15%); seven vertebrae were fractured, mostly located at the thoracic spine (n=6/7), and of grade 1 (n=6/7).

Conclusion In the DESIR cohort, a population of early SpA, we found a low prevalence and incidence of VFs (3.0% and 1.15 %), respectively. This confirms our hypothesis that the actual prevalence and incidence of VFvertebral fracture in SpA is lower than that reported in the previous studies.

Key messages

What is already known about this subject?
- An increased risk of vertebral fractures (VFs) has been reported in spondyloarthritis (SpA).
- However, the prevalence of VFs in patients with axial SpA is highly variable in different studies.

What does this study add?
- In this cohort of early SpA, the prevalence and incidence of VF in SpA was lower than that reported in previous studies.
- These discrepancies can be explained by the differences in the characteristics of the population and the methods of VF assessment.

How might this impact on clinical practice or future developments?
- Deformities of vertebral bodies are frequent in axial SpA, particularly at the thoracic spine, and some deformities may be confounded as a fracture, leading to an overestimation of fracture.
- This should be taken into account for the diagnosis of VF.

BACKGROUND

Osteoporosis is a frequent complication of inflammatory rheumatic disorders and a well-recognised feature of axial spondyloarthropathy (axial SpA).[1] The disease is characterised by osteoporosis, osteoproliferation and spine ankylosis. The ankylosed spine is at risk of fractures. A case–control study of 53 108 patients with fractures using the Swedish National Hospital Discharge Register showed that the risk of fractures was higher in SpA than in rheumatoid arthritis (RA), and that the largest increase was for vertebral fracture (VF) (OR 7.1 and 2.7 for SpA and RA, respectively).[2] However, decreased mobility might not be the single mechanism of bone fragility because low bone mineral density has also been observed in patients with early SpA.[3] Systemic inflammation itself has a deleterious effect on bone remodelling, and this is the rationale for studying the potential positive bone effects of potent anti-inflammatory drugs.[4–6]

The prevalence of VFs in patients with axial SpA is highly variable in different studies, up to 30%.[7–9] These data are unexpected in a disease affecting a young population, predominantly males and without treatment with glucocorticoids. Actually, the definition of a VF varies among studies. The objective of our study was to assess the incidence of VFs in a cohort of early inflammatory back pain suggestive of early axial SpA over 5 years.

METHODS

Population

The DESIR (DEvenir des Spondylarthropathies Indifférenciées Récentes) cohort is a longitudinal prospective cohort studying subjects with inflammatory back pain (IBP) of recent onset and recruited from 25 regional centres in France. A detailed description of the centres, organisation of the cohort and full detailed protocol are available

online (http://www.lacohortedesir.fr).[10] The cohort included patients aged over 18 years and under 50 years with IBP as defined by Calin and/or Berlin criteria for more than 3 months and less than 3 years and symptoms suggestive of SpA according to the local rheumatologist's assessment (eg, score ≥5 on a numerical rating scale of 0–10, where 0 is not suggestive and 10 is very suggestive of SpA).[11]

The exclusion criteria were other spinal disease clearly defined (eg, discarthrosis), history of any biotherapy, and history or current disorders that might interfere with the validity of the informed consent and/or prevent optimal compliance of the patient with the cohort. Corticosteroid intake was permitted only in doses of less than 10 mg prednisone per day and had to be stable for at least 4 weeks before baseline. A total of 708 patients with IBP were included between October 2007 and April 2010. Patients were evaluated every 6 months during the first 2 years and then on a yearly basis for an expected total follow-up duration of 10 years. For this study, we used the baseline data of the cohort. For the assessment of the VF, we used the X-rays of baseline and 5 years.

Parameters collected

Baseline parameters were activity and severity parameters of the disease using questionnaires self-assessed by the patient: BASDAI (Bath Ankylosing Spondylitis Disease Activity Index (0–100)), BASFI (Bath Ankylosing Spondylitis Functional Index (0–100)) and medication including use of non-steroidal anti-inflammatory drugs (NSAIDs) and TNF blocker use.[12–15] Risk factors for osteoporosis were assessed at baseline: age, gender, current smoking, height, weight and Body Mass Index (BMI, kg/m^2) were collected. Erythrocyte sedimentation rate and C reactive protein (CRP) were assessed at baseline. The structural damage at spine was evaluated on X-rays by the modified Stokes Ankylosing Spondylitis Spinal Score (mSASSS).[16] The structural damage at the sacroiliac joint was evaluated by the modified New York criteria. The SpondyloArthritis Research Consortium of Canada method was used for scoring inflammation using MRI.[17]

Bone mineral density (BMD) measurements

BMD was measured by dual-energy X-ray absorptiometry at baseline for all included patients in 12 centres (ie, half of the participating centres) with investigators having expertise in BMD measurements. BMD was determined at the lumbar spine (second to fourth vertebrae) and the upper part of the left femur (total femur and femoral neck). The results were given as BMD (g/cm^2), Z and T scores. The International Society of Clinical Densitometry recommends using the threshold of −2 SD in Z score for the definition of low BMD[18] in young adults. Z scores were determined according to references provided by the manufacturers. All examinations were performed according to the manufacturer's recommendations. Devices were controlled by measuring a spine phantom at least three times a week throughout the study; all examinations were performed according to the manufacturer's recommendations.

VF diagnosis

For the assessment of VF, anteroposterior and lateral views of the entire thoracic and lumbar spine were considered. All radiographs of the DESIR cohort (baseline and 5 years) were assessed at a central facility (by a single investigator specialised in the field of the diagnosis of VFs) from the fourth thoracic vertebra to the fourth lumbar vertebrae according to Genant's method.[19–21]The semiquantitative grading scale is as follows: normal, grade 0; mild fracture, a decrease in any vertebral body height of 20% to 25% (grade 1); moderate fracture, a decrease of 25% to 40% (grade 2); and severe fracture, a decrease of 40% or more (grade 3). We used the same method (and definition of height reduction) to define a prevalent VF (present at baseline) and an incident VF. Using a temporal sequence of reading (ie, unblinded for chronological order), an incident VF was defined as a change in the score of a vertebra from grade 0 to a subsequent grade 1 or more at 5 years. In doubtful cases, adjudication by two other senior experts was performed. Careful attention was paid to discriminate vertebral deformities (VDs) of non-osteoporotic origin and VFs as aspects of vertebrae are modified by acquired or constitutional deformations. The deformations due to an infection, a tumour and a metabolic disease are more easily moved away. Among the vertebral height decreases, it is necessary to eliminate those who are not of osteoporotic origin: bad quality of the acquisition with excessive obliquity of the incidental beam responsible for an overlap endplate, a disease of Scheuermann and Schmorl nodes, degenerative deformations of discarthrosis and the variants of normality as short vertebral height. To diagnose a VF from a VD, we use the classification of Genant taking care of decreases superior to 20% but not due to fracture and the fractured decreases not reaching the 20% threshold.[21] We also use the presence of a cortical defect, a depression of a vertebral endplate, an angulation of the endplate and the comparison with vertebrae of the over and under levels. Deformities of similar appearances or contiguous vertebrae and presence of degenerative changes on adjacent intervertebral discs were considered for the deformity origin.

Statistical analysis

Data are expressed as mean (±SD). Analysis on VFs was based on patients having a baseline and a 5-year X-ray follow-up. We assessed the incidence of VFs and VDs and the prevalence of VFs (at least one grade 1) and VDs at baseline and over 5 years. The database used in our study was locked on 30 June 2015 (intended follow-up of the cohort: 10 years). All analyses were performed using SAS software, V.9.1.

RESULTS

Characteristics of the population

Seven hundred and eight (n=708) patients with IBP highly suggestive of axial SpA were included in the DESIR cohort. Six hundred and ninety-four patients had spinal X-rays at baseline and 432 patients had also X-rays at the 5-year visit. This population of 432 patients (mean age was 34.3 (±8.7) years, 53% women) was the basis of our study to assess the incidence of VFs. Their baseline characteristics are described in table 1; they were not different from the DESIR population. For the assessment of the prevalence of VFs and deformities, we used the 262 patients who had spinal X-rays at baseline. Their characteristics are similar to the DESIR population (table 1). A total of 197 patients (45.60%) received a TNF blocker therapy during the 5-year follow-up. BMD measurements were available for 223 patients at baseline and 14.3% had a low BMD defined by a Z-score ≤−2 at at least one site.

Prevalence of VFs and deformities

At baseline, 21 patients had prevalent VFs (3.0%); all of them were located at the thoracic spine; 14 were grade 1 and six grade 2 and one grade 3. VFs were not associated with larger occiput-to-wall distance. Sixty-six patients (9.5%) had a VD which was not a VF. In patients with a higher confidence for the diagnosis

Table 1 Characteristics of the DESIR (DEvenir des Spondylarthropathies Indifférenciées Récentes) population and of analysis population

	Total population N=708	Patients with radiographic follow-up N=432	Patients without radiographic follow-up N=262
Age (years) (mean±SD)	33.74 (8.63)	34.27 (8.66)	32.90 (8.54)
Gender (female, %)	381 (53.8%)	230 (53.24%)	151 (54.7%)
Menopausal status (n, %)	17 (4.46%)	10 (4.35%)	7 (2.6%)
BMI (mean±SD)	23.99 (4.64)	23.94 (4.13)	23.82 (3.9)
CRP (mean±SD)	7.90 (13.54)	7.88 (13.40)	7.93 (13.7)
BASDAI (mean±SD)	44.70 (20.00)	43.53 (19.90)	46.53 (20.0)
BASFI (mean±SD)	30.45 (22.75)	29.46 (22.59)	31.99 (22.96)
Prevalence of IBD	35 (4.94%)	24 (5.56%)	11 (4.2%)
Disease duration (years)	1.51 (0.87)	1.49 (0.89)	1.55 (0.84)
Past use of corticosteroids (n, %)	93 (13.13%)	55 (12.73%)	38 (14.5%)
Score NSAIDs (mean±SD)	44.72 (40.46)	46.05 (39.64%)	42.63 (41.70)
Use of at least one anti-TNF treatment during the 5 years (n, %)	258 (36.44%)	197 (45.60%)	61 (23.30%)
Lumbar spine BMD l (mean±SD)	1.07 (0.16)	1.07 (0.17)	1.07 (0.15)
Hip BMD (mean±SD)	0.99 (0.14)	1.00 (0.14)	0.91 (0.14)
Femoral neck BMD (mean±SD)	0.92 (0.15)	0.98 (0.13)	0.91 (0.14)
Presence of Z score < or =–2 at least one site (n, %)	46 (6.49%)	34 (7.87%)	12 (4.58%)
mSASSS baseline (mean±SD)	0.49 (1.83)	0.50 (1.48)	0.49 (2.29)
SIJ SPARCC score baseline (mean±SD)	4.87 (9.04)	5.43 (9.50)	3.91 (8.15)
HLA B27 antigen (n, %)	410 (57.99%)	268 (62.04%)	142 (54.2%)
Current smoking (n, %)	257 (36.35%)	158 (36.57%)	99 (37.78%)

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BMD, bone mineral density; BMI, Body Mass Index; CRP, C reactive protein; IBD, inflammatory bowel disease; mSASSS, modified Stokes Ankylosing Spondylitis Spinal Score; NSAID, non-steroidal anti-inflammatory drug; SIJ, sacroiliac joint; SPARCC, SpondyloArthritis Research Consortium of Canada; TNF, tumour necrosis factor.

of SpA (≥8) (n=328), the proportion of patients with at least one prevalent VF was 1.8% (n=6) and with at least one VD was 7.9% (n=26). Most frequent causes of VDs were a disease of Scheuermann and Schmorl nodes (n=24), short vertebral height (SVH) (N=21), degenerative deformations of discarthrosis (n=9) and kyphosis/scoliosis (n=4), structural changes related to SpA (squaring, discitis) (n=6), error of parallax (n=2) and presence of a meganucleus (n=1) (online supplementary figures 3–5).

Prevalence of VFs was not different in patients with and without structural damage in sacroiliac joints. Among the 21 prevalent VFs, 4 VFs (19.0%) were found in patients with r-axSpA and 17 in the patients nr-axSpA (p=0.431). Mean values of mSASSS were 0.357 (0.59) in patients with prevalent VF and 0.500 (1.86) in patients without (p=0.04). However, there is the question of clinical relevance of a difference of 0.15 points over a score of 0 to 72. Among 21 prevalent VFs, 20 were observed in patients with NSAIDs and 1 without NSAIDs.

Incidence of VFs and VDs

Diagnosis of VF was doubtful and needed adjudication for 19 patients (4.4%). At 5 years, five patients had an incident VF (1.15%), in a total of seven vertebrae. They were mostly located at the thoracic spine (n=6/7). Most of them were grade 1 (n=6/7) and one VF was a grade 2 (figure 1).

The incidence of vertebral deformities over 5 years was 2.30% and a total of 14 VDs (figure 2). All of them were located at the thoracic spine and were explained by either degenerative changes (discarthrosis) (N=5), increase in kyphosis (N=4) and structural changes related to SpA (squaring, discitis) (N=5).

In patients with a higher confidence for the diagnosis of SpA (≥8) (n=328), the proportion of patients with at least one incident VF was 1.4% (n=3) and at least one incident VD was 3.7% (n=8).

Patients with incident VFs were not different from patients with incident deformities for age (34.9±5.6 and 32.9±8.1 years) and BMI (21.6±2.3 and 22.3±3.7 kg/m^2, respectively). In contrast, a low BMD (Z score ≤−2) was observed in 50% and 16.7% of patients with incident VFs and VDs, respectively. Incidence of VFs was not different in patients with and without structural damage in sacroiliac joints. Among the five incident VFs, two were observed in patients with r-axSpA and three in patients with nr-axSpA (p=0.232). The mean values of mSASSS

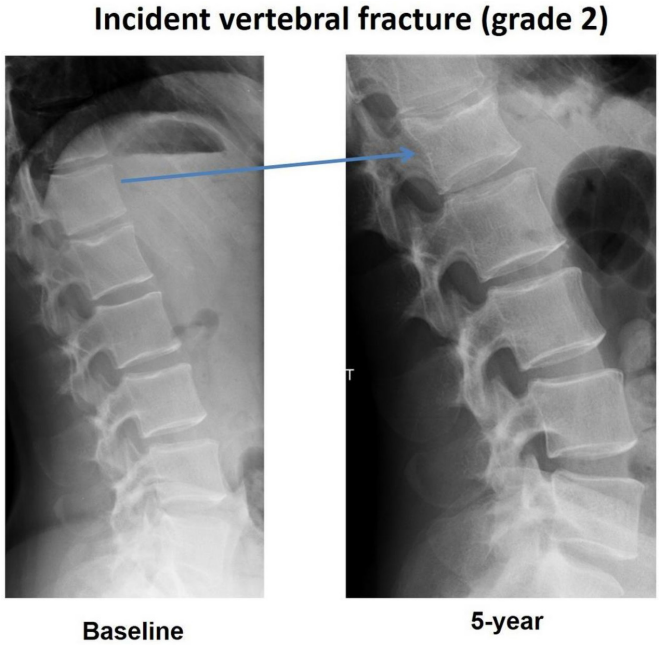

Figure 1 Incident vertebral fracture on spine radiographs.

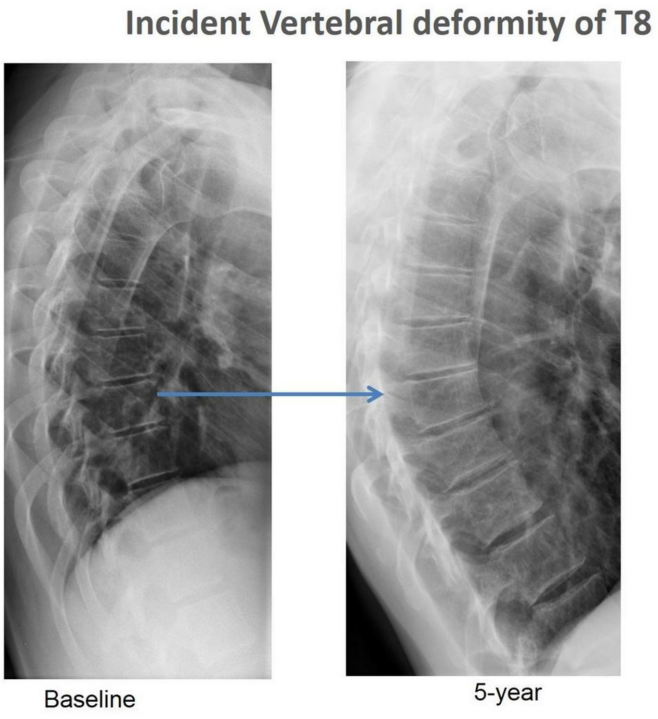

Figure 2 Incident vertebral deformity on spine radiographs.

were similar between patients with and without incident VFs (0.500 (1.0) vs 0.496 (1.48); p=0.806). None of the risk factors attributable to SpA (age, BASDAI, BASFI, CRP, mSASSS) was associated with the presence of incident VFs. The 5 incident VFs and the 14 incident VDs were observed in patients with NSAIDs. Among five incident VFs, three occurred in patients receiving TNF blocker and two without (no statistical difference).

DISCUSSION

This study conducted in a large cohort of young adults with early IBP suggestive of SpA followed in tertiary centres showed a very low incidence of VFs (1.15%). Most of these VFs were mild (grade 1), located at the thoracic spine and occurred in patients without any prevalent VFs.

Both the prevalence and the incidence of VFs reported in our study are lower than that reported in previous studies. Prevalence of VFs ranges from 4% to 42%.[22–28] Data from large databases assessed the relationship between SpA and clinical VFs.[29 30] A nested case–control study performed in the large General Practice Research Database showed that patients with SpA have a threefold increased risk of clinical VF (OR 3.26 (1.51–7.02)).[29] In a large database in Catalonia, Spain, accounting for 80% of the population (6474 patients with axial SpA followed for a median time of 5 years), 0.86% and 3.4% sustained a clinical vertebral and a non-vertebral fracture, respectively. This represents a twofold increased risk of clinical VFs, as compared with controls.[30] In this study, the association between SpA duration and clinical spine fractures was strongest in the first year (OR 8.03 (2.13–30.3)) (short-term SpA ≤1 year since diagnosis), significant for midterm duration (OR 7.52 (1.46–38.8)) and not significant for long-term duration (OR 3.01 (0.87–10.4)). For these two studies, the population was recruited from database with retrospective analysis of data, precluding accurate diagnosis of a flare of the disease or an incident VF as a determinant of pain.

The prevalence of VFs is higher in longstanding SpA disease. In 176 patients (79% men, aged 48.6±13.1 years), with a mean disease duration of 22 years, the prevalence of VFs using a semiautomated software was 32.4%, 82% of the fractures were at the thoracic spine and 65% of them were mild. In a large prospective cohort of 292 patients (mean age of 42.8 years, 70% men) with ankylosing spondylitis (mean time since the diagnosis of 6 years and a mean duration of symptoms of 16 years), 15 (6%) developed new VFs over 2 years.[24] Most fractures were mild and located at the midthoracic and thoracolumbar regions of the spine.[24] In this study, VFs were frequently observed in older patients, with advanced disease, low hip BMD and less healthy life. In patients with early SpA (7 months of disease duration but 5.7 years of symptom duration), 15% of the 113 patients (66% men, age 37.3±9.0 years) had a vertebral fracture; most of them were located at the mid-thoracic spine, half of the fractures were moderate and none were severe.[23] These VFs were associated with low BMD of the lumbar spine and with axial psoriatic arthritis.

These discrepancies might be explained by the characteristics of our population: 53% of them were women with a symptom duration of 12 months on average and 45% of them used biologics during the 5 years of follow-up. There is no evidence that these treatments have an antifracture efficacy, but it has been reported in different studies and in patients with different disease duration that these treatments increase BMD, a surrogate marker of bone strength. In our study, prevalent and incident VFs were observed in patients receiving NSAIDs and TNF blockers, even if it is impossible to definitively conclude because of the low number of incidental events. Unlike other studies,[23 24] we did not identify any risk factors of VF related to SpA disease but the small number of events, making impossible any definitive interpretation. These discrepancies can also be explained by the different methods used for vertebral fracture diagnosis (semiautomated, semiquantitative, qualitative, etc). VFs are often defined in studies as a reduction in vertebral height relative to the other vertebrae, but this definition does not consider the deformities of vertebral bodies. Hence, some deformities associated with the disease may be confounded as a fracture, leading to an overestimation of fracture.[31]

Deformities of vertebral bodies are frequent in axial SpA, particularly at the thoracic spine, for various reasons: erosions of the anterior corners, squaring, wedging secondary to discitis and so on. In our study, we showed that the main causes of vertebral deformities were SVH and Scheuermann disease. These deformities are captured by semiautomated methods of morphometry, which use automatically positioning of points on vertebral contours; with such methods, 'fractures' are defined as any reduction of the anterior or middle height of the vertebral body higher than 20% as compared with the posterior height, or adjacent vertebral body heights. These methods are very sensitive but need expert adjudication; otherwise, they increase the risk of false positives.[32] Moreover, the thoracic and lumbar vertebrae can be normally wedged and biconcave, respectively. SVHs are frequent at the thoracic spine and are not related to osteoporosis or fracture risk.[31] Knowing that, we paid attention to direct and indirect signs of endplate fracture mainly at the middle part of the vertebral body. The necessity of the vertebral endplate depression for the VF diagnosis at the thoracic level permits the elimination the non-osteoporotic VDs. However, this depression is much more difficult to appreciate at the lumbar spine where the vertebra is spontaneously biconcave. Moreover, in men, there are difficulties in the diagnosis of VFs because of the frequency of the non-osteoporotic VD due to traumatisms, disc and vertebral degeneration, and lesions secondary to Scheuermann disease.[19]

VFs are the hallmark of osteoporosis, and it has been shown that the presence of VFs is the main determinant of the risk of future osteoporotic vertebral and non-vertebral fractures. The strongest

associations were observed between prior and subsequent VFs, and this risk increases with the number of prior vertebral fractures.[33–35] Low BMD is also a strong risk factor of future fracture, with a strong relationship between the decrease in BMD and the risk of further fracture.[36] We observed that the proportion of patients with osteoporosis was higher in patients with incident VFs than in other patients, but the very low number of events preclude any analysis of other risk factors. In our study, most of the VFs were mild (grade 1). Such deformities are sometimes considered as an expected effect of ageing in osteoporotic patients, which is not a hypothesis in our study conducted in a young population. The relevance of mild VFs has been shown in studies conducted in osteoporotic postmenopausal women showing in this population that these mild fractures are a risk factor for sustaining other VFs.[20 37] However, their relevance in young adults needs further studies.

The strengths of our study were that we had a large prospective cohort of axial SpA over 5 years, we made a careful interpretation of every X-ray using a semiquantitative method and if needed we made adjudication for doubtful cases in few cases (4.4%). We confirmed the prevalence and incidence of VFs and VDs in patients with a higher confidence of the axSpA diagnosis (eg, ≥8). The limits of this study were the small number of events, making impossible the interpretation of some secondary analysis, like the identification of risk factors for VFs. It will be interesting to use the MRI follow-up to distinguish VDs and VFs, but MRI is only available for 190 patients at 5 years.

We found in the DESIR cohort, a population of early SpA, a prevalence of VF of 3.0% and 1.15% of incidental VFs. This confirms our hypothesis that the actual prevalence and incidence of VF in SpA is lower than that reported in previous studies, probably depending on the characteristics of the population and the methods of vertebral fracture's assessment avoiding any misclassification of VDs.

Correction notice This article has been corrected since it published Online First. The sixth author's name has been corrected to Pascal Richette.

Acknowledgements The DESIR study is conducted as a Programme Hospitalier de Recherche Clinique with Assistance Publique Hopitaux de Paris as the sponsor. The DESIR study is also under the umbrella of the French Society of Rheumatology, which financially supports the cohort. An unrestricted grant from Pfizer has been allocated for the first 5 years. The DESIR cohort is conducted under the control of Assistance Publique Hopitaux de Paris via the Clinical Research Unit Paris Centre and under the umbrella of the French Society of Rheumatology and Institut national de la sante et de la recherche medicale (Inserm). Database management is performed within the Department of Epidemiology and Biostatistics (Professeur Jean-Pierre Daures, DIM, Nımes, France). We also wish to thank the different regional participating centres: MD (Paris-Cochin B), Andre Kahan (Paris-Cochin A), Philippe Dieudé (Paris-Bichat), Bruno Fautrel (Paris-La Pitie-Salpetriere), Francis Berenbaum (Paris-Saint-Antoine), Pascal Claudepierre (Creteil), Maxime Breban (Boulogne-Billancourt), Bernadette Saint-Marcoux (Aulnay-sous-Bois), Philippe Goupille (Tours), Jean Francis Maillefert (Dijon), Emmanuelle Dernis (Le Mans), Daniel Wendling (Besancon), Bernard Combe (Montpellier), Liana Euller-Ziegler (Nice), Pascal Richette (ParisLariboisiere), Pierre Lafforgue (Marseille), Patrick Boumier (Amiens), Martin Soubrier (ClermontFerrand), Nadia Mehsen (Bordeaux), Damien Loeuille (Nancy), Rene-Marc Flipo (Lille), Alain Saraux (Brest), Xavier Mariette (LeKremlin-Bicetre), Alain Cantagrel (Toulouse) and 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 Nımes and all the investigators, and in particular Jerome Allain, Emmanuelle Dernis, Salah Ferkal, Clement Prati, Marie-Agnes Timsit and Eric Toussirot, for active patient recruitment and monitoring.

Contributors The author and the coauthors contributed equally to this paper: design of the work, analysis and/or interpretation of data, drafting the work or revising it critically, and final approval of the version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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