RHEUMATOLOGY

Rheumatology 2022;61:3279–3288
https://doi.org/10.1093/rheumatology/keab887
Advance Access publication 30 November 2021

Original article

Peripheral manifestations are major determinants of disease phenotype and outcome in new onset spondyloarthritis

Ann-Sophie De Craemer [1,2], Thomas Renson[1,2], Liselotte Deroo[1,2], Liesbet Van Praet[3], Heleen Cypers[4], Gaëlle Varkas [1], Rik Joos[1,5], Mieke Devinck[6], Lieve Gyselbrecht[7], Isabelle Peene[1,8], Kristof Thevissen[4,9], Félicie Costantino [10,11], Maria-Antonietta D'Agostino[10,11,12], Jan Lenaerts[13,14], Philippe Carron[1,2,15], Filip Van den Bosch[1,2,*] and Dirk Elewaut[1,2,*]

Abstract

Objectives. To delineate the impact of peripheral musculoskeletal manifestations on stratification of disease phenotype and outcome in new-onset spondyloarthritis (SpA), using a prospective observational nationwide inception cohort, the BelGian Inflammatory Arthritis and spoNdylitis cohorT (Be-Giant).

Methods. Newly diagnosed adult SpA patients, fulfilling the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial or peripheral SpA, were included in Be-Giant and prospectively followed every six months. Peripheral involvement (defined as arthritis, enthesitis and/or dactylitis) was determined in relation to clinically similar patient subsets at baseline and disease activity patterns during two-year follow-up, identified through K-means cluster analysis and latent class growth analysis.

Results. From November 2010 to March 2020, 367 patients were enrolled in Be-Giant, of whom 162 (44%) had peripheral manifestations. Two patient clusters [A, axial predominant ($n = 248$) and B, peripheral predominant ($n = 119$)] were identified at diagnosis. Longitudinal analysis ($n = 115$) revealed two trajectories of disease activity in each cluster: one with persistently high disease activity over time ('High'), the other rapidly evolving to low disease activity ('Low'). In cluster A patients, peripheral manifestations predisposed to the 'High' trajectory [odds ratio (OR) = 2.0, 95% CI: 1.3, 3.1, $P = 0.001$], despite more rapid initiation of biologics compared with patients without peripheral manifestations (hazard ratio (HR) = 2.1, 95% CI: 1.0, 4.4, $P = 0.04$ – Cox proportional-hazards model).

Conclusion. Peripheral musculoskeletal manifestations are major determinants of phenotypical diversity in new-onset SpA. Intriguingly, stratification of axial SpA according to concomitant peripheral involvement identified an endotype with an unfavorable outcome despite more prompt therapeutic intensification with biologics. These observations justify an endotype-tailored approach beyond current ASAS/EULAR management recommendations.

Key words: spondyloarthritis, peripheral manifestations, clusters, trajectories

[1]Department of Internal Medicine and Pediatrics, Division of Rheumatology, Ghent University Hospital, Gent, [2]Center for Inflammation Research, VIB-UGent, Zwijnaarde, [3]Department of Rheumatology, AZ Maria Middelares, [4]Reumacentrum Genk, Genk, [5]Department of Rheumatology, ZNA Jan Palfijn, Merksem, [6]Department of Rheumatology, AZ Sint-Lucas, Assebroek, [7]Department of Rheumatology, Algemeen Stedelijk Ziekenhuis (ASZ), Aalst, [8]Department of Rheumatology, AZ Sint-Jan, Brugge, [9]Department of Rheumatology, Ziekenhuis Oost-Limburg (ZOL), Genk, Belgium, [10]Université Paris-Saclay, UVSQ, Inserm U1173, Infection et inflammation, Laboratory of Excellence INFLAMEX, Montigny-Le-Bretonneux, [11]Rheumatology Department, AP-HP, Ambroise Paré Hospital, 92100, Boulogne-Billancourt, France, [12]Rheumatology Department, Università Cattolica del Sacro Cuore, Policlinico Universitario Agostino Gemelli IRCSS, Roma, Italy, [13]Reuma Instituut, [14]Department of Rheumatology, AZ Jessa Hospitals, Hasselt and [15]Department of Rheumatology, AZ Alma, Eeklo, Belgium

Submitted 27 August 2021; accepted 20 November 2021

Correspondence to: Ann-Sophie De Craemer, Department of Internal Medicine and Pediatrics, Division of Rheumatology, Ghent University Hospital, C. Heymanslaan 10, 9000 Gent, Belgium.
E-mail: annsophie.decraemer@ugent.be

*Filip Van den Bosch and Dirk Elewaut contributed equally to this study.

Rheumatology key messages

- Cluster analysis divides the SpA spectrum in an axial or peripheral predominant phenotype at diagnosis.
- Longitudinal follow-up reveals two distinct patterns of disease activity in each cluster.
- Clinical clues (i.e. concomitant axial and peripheral disease) support endotype-based patient stratification.

Introduction

Spondyloarthritis (SpA), a heterogeneous group of chronic immune-mediated inflammatory conditions, represents a commonly encountered rheumatic disease with potential impact on patients' physical, emotional and societal well-being [1]. The SpA concept covers symptoms associated with spinal, joint and entheseal inflammation, besides extra-musculoskeletal manifestations such as acute anterior uveitis (AAU), psoriasis and IBD [2].

The diagnostic and therapeutic approach in SpA has previously been determined by prototypic diseases like ankylosing spondylitis (AS) and PsA. However, in 2009, the Assessment of SpondyloArthritis International Society (ASAS) developed new classification criteria that acknowledged SpA as a single condition, albeit with predominant axial or peripheral symptomatology [3, 4]. Inherent to the concept of a disease spectrum, a considerable overlap between axial and peripheral symptoms can be observed in a subgroup of patients. They are currently classified as axial SpA (axSpA) with peripheral involvement, independent of the most disabling symptom. A recent study revealed that half of the patients who are classified as axSpA indeed show one or more peripheral manifestations, contributing significantly to the overall disease activity [5]. Whether this impacts long-term outcomes is, however, poorly studied. The failure to recognize these clinically important nuances could be due to the current—widely adopted—binary classification. Notably, the ASAS classification co-exists with the ClASsification criteria for PsA (CASPAR), with peripheral PsA being the most studied peripheral SpA (pSpA) subtype [6].

Few studies have addressed the diagnostic and prognostic value of peripheral manifestations, considering the entire SpA spectrum. This study therefore aimed to explore their prevalence in newly diagnosed SpA patients, their contribution to baseline clinical phenotyping, and their predictive value in relation to trajectories of disease activity and associated therapeutic implications during the first two years of follow-up.

Patients and methods

Study design

Clinical data originated from the Be-Giant (BelGian Inflammatory Arthritis and spoNdylitis cohorT), a Belgian multicentre prospective observational cohort of newly diagnosed SpA patients. From November 2010, eligible patients were enrolled at the rheumatology outpatient clinic of one academic and nine peripheral hospitals no more than one year after the diagnosis. The Be-Giant's global objective consists of providing accurate data on the epidemiology and disease course (clinical and radiographic evolution) of newly diagnosed SpA patients in Belgium since the introduction of the ASAS classification criteria [3, 4], which facilitated early diagnosis. Enrolment of new patients is still ongoing.

Adult patients with an expert opinion diagnosis of SpA were consecutively included if they fulfilled the ASAS classification criteria for axSpA or pSpA [3, 4]. Exclusion criteria were previous exposure to biological disease-modifying anti-rheumatic drugs (bDMARD, e.g. for non-SpA indications such as psoriasis or IBD) and the presence of syndesmophytes on spinal radiographs, which was considered indicative of advanced axial disease. Experienced rheumatologists performed a comprehensive patient description at baseline, followed by a systematic follow-up with six-month intervals.

All patients provided written informed consent. The ethical review boards of Ghent University Hospital and every participating center (ZNA Jan Palfijn Merksem, ASZ Aalst, AZ Alma Eeklo, AZ Sint-Lucas Assebroek, AZ-Sint Jan Brugge and AZ Maria Middelares Gent) approved this study, which was executed according to the Declaration of Helsinki and Good Clinical Practice standards. Patients were not involved in the design or the conduct of this study.

Clinical assessment

Data collected at baseline comprised demographics, personal and family medical history, previous and concomitant medication (including the use of and response to NSAIDs), alcohol use, smoking status, inflammatory back pain (IBP) features and HLA B27 status. The treating rheumatologist documented peripheral manifestations (defined as arthritis, enthesitis or dactylitis) only in case of sufficient clinical and/or imaging evidence at the baseline visit or at an earlier time point. Enthesitis in particular was an expert opinion diagnosis. Thus, pain elicited by local pressure on a limited number of entheseal sites as evaluated by the Maastricht AS Enthesitis Score (MASES) was neither necessary nor sufficient [7]. By convention, arthritis was documented in digits affected by dactylitis. Diagnosis of present or prior extra-musculoskeletal manifestations required the confirmation by a respective specialist. Clinical examination comprised the assessment of weight (kg) and height (cm),

linear Bath AS Metrology Index (BASMI), 78/76 tender and swollen joint count (TJC/SJC), MASES + plantar fascia and dactylitic digits. Patient reported outcomes (PRO) consisted of the Bath AS Disease Activity Index (BASDAI) and the Bath AS Functional Index (BASFI). The patient's and physician's global assessment of disease activity (PGA and PhGA) and the patient's pain scores were assessed on a numeric rating scale (0–10). Finally, ESR (mm/h) and CRP (mg/l) were recorded, and the AS Disease Activity Score (ASDAS) was determined [8–10].

At follow-up visits, patients were systematically questioned about axial, peripheral or extra-musculoskeletal symptoms besides therapeutic modifications in the previous six months. Baseline clinical examination, PRO and laboratory investigations were consistently repeated.

Statistical analysis

Statistical analyses were performed using R (version 4.0.2) and RStudio. Continuous variables were compared using the Student's-T or Wilcoxon rank-sum test in case of small and non-normally distributed variables. Proportions were compared with the χ^2 or Fisher's exact test. Regarding the initiation of bDMARDs, patient groups were compared by a time-to-event analysis (survival analysis) whereby a Cox proportional-hazards model estimated the effect of peripheral involvement on bDMARD initiation. Statistical tests were two-sided; *P*-values <0.05 were considered statistically significant.

Two multivariate approaches were applied to identify and group SpA patients with similar profiles in terms of clinical characteristics (at baseline) and evolution of disease activity (longitudinal analysis from baseline until two years of follow-up).

Cluster analysis, an unsupervised classification method that groups patients with similar characteristics, relied on 15 baseline demographic and clinical variables, congruent with the ASAS classification features. A first step consisted of dimension reduction and imputation of missing values using factor analysis for mixed data (FAMD, R packages *FactoMineR* and *missMDA*). In a second step, partition-based K-means clustering was performed on the FAMD coordinates of the individual observations. The optimal number of clusters was chosen according to the 'elbow method', the silhouette coefficient and the gap statistic [11]. Stability of the cluster configuration was verified by 100 bootstrap iterations, calculating the Jaccard similarity coefficients between the original clusters and the most similar ones obtained from the resampled data [12]. Jaccard coefficients >0.75 were considered to indicate stable clusters.

Latent class growth analysis grouped patients with shared trajectories of disease activity (i.e. latent classes) during the first two years of follow-up (R package *lcmm*). ASDAS-CRP was chosen as the dependent outcome variable because it is a validated measure for disease activity, containing both an axial and peripheral disease component besides an objective inflammatory marker [8]. In contrast to the cluster-based approach at baseline, longitudinal patient trajectories were identified according to a model-based approach, which has some advantages over longitudinal clustering techniques such as formal statistics to choose the optimal number of classes and probability-based classification allowing to generalize the results to a broader population [13]. One to six classes were tested, each for three distinct polynomial trajectory shapes: linear, quadratic and cubic. Model parameters were based on maximum likelihood estimation. Each model was run 100 times with varying start values based on the 1-class model [14]. The optimal model was chosen according to statistical fit and clinical relevance. Baseline clinical characteristics were compared between trajectories using binomial (logit) regression.

Results

Baseline characteristics

On 1 March 2020, the Be-Giant cohort included 367 newly diagnosed SpA patients: 257 (70%) and 110 (30%), respectively, fulfilled the ASAS axSpA and pSpA classification criteria. A total of 190 of 367 (52%) were male with a mean (S.D.) age of 34 (10.9) years. Peripheral manifestations were present at or prior to baseline in 162 of 367 (44%) patients. These comprised 52 of 257 (20%) axSpA classified patients and 110 pSpA classified patients, among which 52 (47%) fulfilled the CASPAR criteria for PsA. Among the 162 patients with peripheral involvement, 143 had arthritis, 52 had enthesitis and 55 had dactylitis (Table 1). Only a minority of patients already presented with peripheral symptoms prior to the SpA diagnosis [26 of 143 (18%) arthritis, 17 of 52 (33%) enthesitis and 5 of 55 (9%) dactylitis] with a median [inter-quartile range (IQR)] diagnostic delay of, respectively, 3 (1–12), 4 (1–22) and 2 (1–5) months. Clinical characteristics of the entire cohort and different subtypes are summarized respectively in Table 1 and Supplementary Table S1, available at *Rheumatology* online.

Baseline cluster analysis

K-means cluster analysis was performed using the baseline clinical features of all Be-Giant patients (Supplementary Table S2, available at *Rheumatology* online). Supplementary Fig. S1A and S1B (available at *Rheumatology* online) show the results of the preliminary FAMD analysis, providing imputation of missing values in 44 of 367 (12%) patients and subsequent dimension reduction. A configuration with two groups, named cluster A ($n=248$) and cluster B ($n=119$), proved to be optimal in terms of minimizing the total within-cluster variation and maximizing cluster stability with median Jaccard coefficients >0.90 (Supplementary Fig. S1C–S1E, available at *Rheumatology* online).

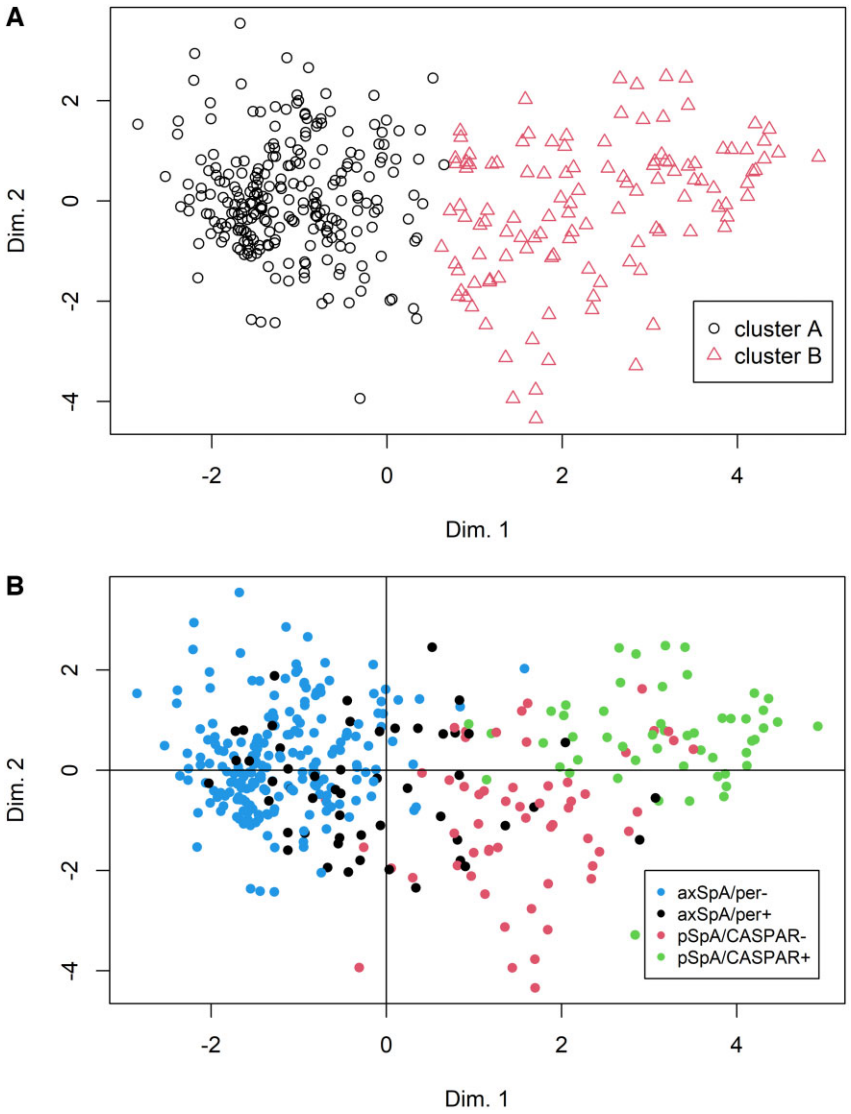
Cluster A mainly consisted of axSpA classified patients [242 of 248 (98%)] while the majority of patients in cluster B were classified as pSpA [104 of 119 (87%)] (Fig. 1). Although patients with peripheral manifestations

Table 1 Baseline demographic and clinical characteristics of patients included in the Be-Giant cohort

	All SpA patients ($n = 367$)	Axial SpA ($n = 257$)	Peripheral SpA ($n = 110$)	*P*-value
Male	190 (51.8)	128 (49.8)	62 (56.4)	0.25
Age, years	34 (10.9)	32 (8.3)	41 (13.3)	**<0.001**
Caucasian ethnicity	349 (95.1)	243 (94.6)	106 (96.4)	0.46
Current alcohol use	302 (83.4)	213 (83.9)	89 (82.4)	0.73
Current smoker	72 (19.9)	52 (20.5)	20 (18.5)	0.67
Symptom duration, months (median, IQR)	14 (4–57)	27 (10–83)	2 (1–9)	**<0.001**
Disease duration, months	1.2 (2.3)	1.4 (2.4)	0.8 (1.8)	**0.005**
HLA B27 positive	228 (64.4)	181 (70.7)	47 (48.0)	**<0.001**
Family history of SpA[a]	140 (38.3)	99 (38.7)	41 (37.3)	0.80
Inflammatory back pain[b]	242 (65.9)	226 (87.9)	16 (14.5)	**<0.001**
Any peripheral manifestation (now/ever)	162 (44.1)	52 (20.2)	110 (100.0)	**<0.001**
Arthritis	143 (39.0)	38 (14.8)	105 (95.5)	**<0.001**
Enthesitis	52 (14.2)	24 (9.3)	28 (25.5)	**<0.001**
Dactylitis	55 (15.0)	5 (1.9)	50 (45.5)	**<0.001**
Any extra-musculoskeletal manifestation (now/ever)	116 (31.6)	63 (24.5)	53 (48.2)	**<0.001**
Psoriasis skin/nails	70 (19.1)	23 (8.9)	47 (42.7)	**<0.001**
Acute anterior uveitis	33 (9.0)	31 (12.1)	2 (1.8)	**0.002**
IBD	17 (4.6)	12 (4.7)	5 (4.5)	0.96
BMI, kg/m^2	24.6 (4.2)	24.3 (4.0)	25.1 (4.4)	0.11
Linear BASMI	2.1 (0.8)	2.1 (0.8)	2.1 (0.9)	0.99
MASES + plantar fascia (median, IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0.48
TJC (median, IQR)	0 (0–3)	0 (0–0)	5 (2–8)	**<0.001**
SJC (median, IQR)	0 (0–1)	0 (0–0)	3 (1–5)	**<0.001**
CRP, mg/l	10.6 (18.9)	7.0 (9.6)	19.1 (29.7)	**<0.001**
Elevated CRP (≥5 mg/l)	159 (43.6)	98 (38.9)	61 (56.0)	**0.002**
ESR, mm/h	17 (18.4)	13 (11.9)	26 (25.7)	**<0.001**
ASDAS-CRP	2.8 (1.0)	2.6 (1.0)	3.1 (1.1)	**<0.001**
DAPSA	—	—	24 (13.1)	**—**
BASDAI	4.5 (2.0)	4.3 (2.0)	4.9 (2.0)	**0.008**
BASFI	3.1 (2.2)	2.8 (2.1)	3.6 (2.4)	**0.003**
PGA	5 (2.9)	5 (2.8)	6 (2.8)	**<0.001**
PhGA	5 (2.6)	4 (2.4)	6 (2.3)	**<0.001**
Patient pain	4 (2.6)	4 (2.6)	5 (2.6)	**0.01**
NSAID use	267 (73.0)	187 (72.8)	80 (73.4)	0.90
NSAID index 1 month prior to baseline	48 (43)	48 (43)	49 (41)	0.86
csDMARD use	24 (6.5)	8 (3.1)	16 (14.5)	**<0.001**
Radiographic sacroiliitis[c]	45 (13.2)	43 (17.9)	2 (2.0)	**<0.001**
Positive MRI-SIJ[c]	233 (69.3)	215 (87.0)	18 (20.2)	**<0.001**

Categorical variables are presented as *n* (%), continuous variables are presented as mean (S.D.) unless indicated otherwise. *P*-values represent comparison of axSpA *vs* pSpA. [a]Presence of ankylosing spondylitis, psoriasis, acute uveitis, reactive arthritis or IBD in a first-degree or second-degree relative. [b]Inflammatory back pain (IBP) according to the ASAS criteria, history of IBP in case of pSpA. [c]Radiographic sacroiliitis according to modified New York criteria and a positive MRI-SIJ according to the ASAS consensus definition as assessed by the local investigator. Data were missing for alcohol use ($n = 5$), smoking status ($n = 5$), HLA B27 status ($n = 13$), family history of SpA ($n = 1$), BMI ($n = 17$), BASMI ($n = 40$), MASES ($n = 9$), CRP ($n = 2$), ESR ($n = 30$), ASDAS-CRP ($n = 23$), BASDAI ($n = 14$), BASFI ($n = 15$), PGA ($n = 21$), PhGA ($n = 6$), NSAID use ($n = 1$), radiographic sacroiliitis ($n = 27$), and positive MRI-SIJ ($n = 31$). ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; csDMARD: conventional synthetic disease modifying anti-rheumatic drugs; DAPSA: Disease Activity in PsA; IQR: inter-quartile range; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; PGA: patient global assessment; PhGA: physician global assessment; SIJ: sacroiliac joints; SJC: swollen joint count; SpA: spondyloarthritis; TJC: tender joint count. Bold type indicates significance.

FIG. 1 Cluster analysis on FAMD coordinates of individual patients included in the Be-Giant cohort



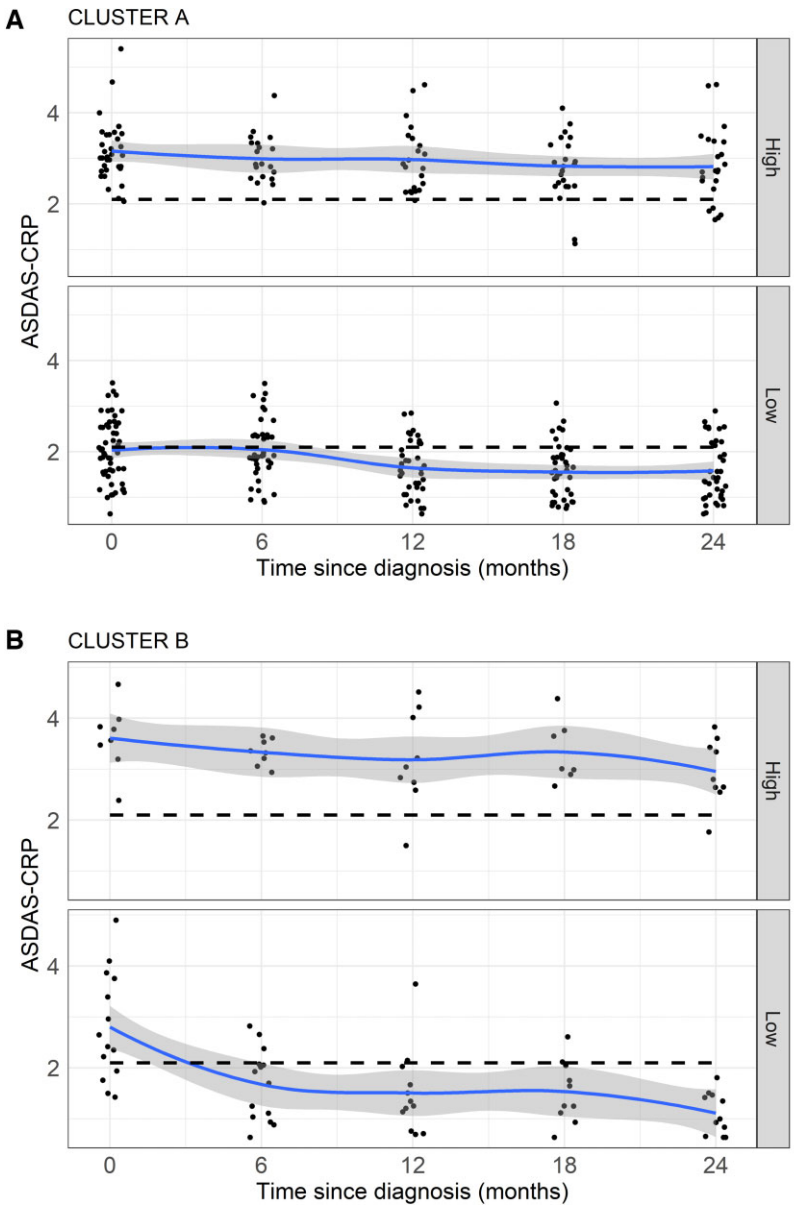
Each symbol/dot represents an individual patient in relation to the first and the second principal dimension; patients with a similar clinical profile are closer to each other. Left panel: colours correspond to different clusters: cluster A (black dots) and cluster B (red triangles); right panel: colours correspond to the individual's classification: axial SpA with or without peripheral manifestations and peripheral SpA with or without fulfillment of CASPAR criteria for PsA.

were primarily allocated to cluster B [117 of 162 (72%)] compared with cluster A [45 of 162 (28%)], 39 of 52 (75%) axSpA classified patients with peripheral involvement were found in cluster A, as well as the majority of IBP patients with peripheral symptoms [40 of 61 (66%)]. Besides IBP, other features typically associated with axSpA such as HLA B27, AAU and sacroiliitis were more abundant in cluster A while psoriasis and older age at symptom onset were more prevalent in cluster B (Supplementary Table S3, available at *Rheumatology* online). Indices of disease activity and functional impairment were significantly higher in cluster B compared with cluster A.

Longitudinal follow-up

Of the 367 patients included in Be-Giant, 195 (53%) attained a follow-up of minimum two years and 115 (31%) attended every follow-up visit. Longitudinal analysis was based on the latter group. Excluded patients participated in a phase III clinical trial ($n = 60$), were lost-to-follow-up ($n = 46$), did not reach two years of follow-up yet ($n = 66$) or did not attend every follow-up visit ($n = 80$). Sensitivity analysis did not indicate clinically significant differences between patients in- and excluded from longitudinal analysis (Supplementary Table S4, available at *Rheumatology* online). ADSAS-CRP values were available from 110

FIG. 2 Distribution of ASDAS-CRP over time across distinct trajectories in cluster A and cluster B



Mean trajectories are constructed with Loess regression (smoothed conditional mean), error bands represent 95% CIs. A reference line was added at y=2.1. ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score—CRP.

(96%), 80 (70%), 79 (69%), 79 (69%) and 81 (70%) patients at baseline, 6, 12, 18 and 24 months, respectively.

Longitudinal analysis identified two clinically relevant trajectories of disease activity in cluster A and cluster B (Supplementary Table S5, available at *Rheumatology* online). In cluster A, the 'High' and the 'Low' trajectory represented respectively 34 (38%) and 55 (62%) of 89 patients. Baseline disease activity was high [ASDAS-CRP 3.2 (1.1)] and remained relatively stable in the 'High' trajectory. Patients in the 'Low' trajectory started at a lower level [ASDAS-CRP 2.0 (1.0)] that declined during follow-up (Fig. 2). Patients in the 'High' trajectory were less frequently male or HLA B27 positive, but were more often affected by peripheral manifestations, which remained a significant predictor in multivariate analysis [odds ratio (OR) = 2.4, 95% CI: 1.5, 3.8] (Table 2). Moreover, bDMARDs [>95% TNF inhibitors (TNFi)] were more promptly initiated in cluster A patients with peripheral manifestations compared with those without (hazard ratio (HR) = 2.1, 95% CI: 1.0, 4.4, P = 0.04, adjusted for csDMARD use). PGA, pain and function scores followed a pattern largely comparable to ASDAS-CRP in the 'Low' trajectory, whereas a slight decrease in these outcomes could be observed in the 'High' trajectory (Supplementary Fig. S2, available at *Rheumatology* online).

Table 2 Baseline demographic and clinical characteristics across trajectory groups in cluster A and cluster B

	Cluster A				Cluster B			
	'High' $n = 34$	'Low' $n = 55$	OR (95% CI)	*P*-value	'High' $n = 9$	'Low' $n = 15$	OR (95% CI)	*P*-value
Male	11 (32)	29 (53)	0.4 (0.3, 0.6)	**<0.001**	3 (33)	9 (60)	0.3 (0.2, 0.7)	**0.005**
Age, years	33 (11.0)	32 (13.4)	1.0 (0.9, 1.0)	0.13	50 (11.6)	44 (18.0)	1.0 (1.0, 1.1)	**0.02**
Symptom duration, months (median, IQR)	27 (8–65)	39 (18–105)	1.0 (1.0, 1.1)	0.14	17 (7–18)	11 (5–35)	1.0 (0.8, 1.1)	0.60
Inflammatory back pain	31 (91)	52 (95)	0.6 (0.3, 1.2)	0.17	1 (11)	2 (13)	0.8 (0.3, 2.5)	0.72
HLA B27	21 (64)	42 (76)	0.6 (0.4, 0.8)	**0.004**	2 (25)	4 (31)	0.8 (0.3, 1.8)	0.53
Peripheral manifestation	10 (30)	9 (16)	2.0 (1.3, 3.1)	**0.001**	9 (100)	15 (100)	—	—
Arthritis	7 (21)	4 (7)	3.7 (2.1, 6.4)	**<0.001**	8 (88)	15 (100)	—	—
Enthesitis	4 (12)	5 (9)	1.4 (0.8, 2.4)	0.21	2 (22)	3 (20)	1.1 (0.5, 2.8)	0.77
Dactylitis	0 (0)	0 (0)	—	—	5 (55)	7 (47)	1.4 (0.7, 3.0)	0.35
PRO[a]								
BASDAI	5.6 (2.5)	3.4 (2.2)	—	—	5.9 (2.8)	4.4 (2.5)	—	—
BASFI	4.3 (2.3)	1.9 (2.1)	—	—	5.6 (2.5)	2.4 (2.3)	—	—
ASDAS-CRP	3.2 (1.1)	2.0 (1.0)	—	—	3.6 (1.2)	2.8 (1.3)	—	—
PGA	7 (3.0)	4 (3.4)	—	—	7 (3.6)	5 (3.4)	—	—
Pain score	6 (2.6)	3 (2.8)	—	—	6 (3.6)	4 (2.8)	—	—
PhGA	5 (3.0)	3 (2.7)	—	—	7 (2.4)	6 (2.6)	—	—
Elevated CRP	12 (35)	12 (22)	1.4 (0.8, 2.3)	0.24	6 (66)	8 (53)	4.3 (1.9, 9.7)	**<0.001**
Positive MRI-SIJ[b]	28 (85)	47 (87)	0.8 (0.5, 1.5)	0.52	2 (25)	4 (36)	0.4 (0.2, 1.0)	0.06
csDMARD initiation[c]	3 (9)	1 (2)	—	—	7 (77)	13 (87)	—	—
bDMARD initiation[c]	18 (53)	20 (36)	—	—	3 (33)	4 (27)	—	—

Odds ratios (OR) are calculated for the 'High' disease activity trajectory, considering the 'Low' trajectory as a reference; *P*-values are given for the ORs. Categorical variables are presented as *n* (%), continuous variables are presented as mean (S.D.) unless indicated otherwise. [a]Patient-reported outcomes (PRO) were not included in the binomial logit regression model as a potential predictor of trajectories because of risk of collinearity, because the trajectories are constructed based on ASDAS-CRP. [b]Positive magnetic resonance imaging of the sacroiliac joints according to the ASAS consensus definition as assessed by the local investigator. [c]cs/bDMARD initiation during two-year follow-up (not a baseline feature). Data were missing in cluster A for HLA B27 status ($n = 1$), BASDAI ($n = 1$), BASFI ($n = 1$), ASDAS-CRP ($n = 1$), PGA ($n = 1$), pain score ($n = 1$), and ASAS positive MRI ($n = 3$), and in cluster B for HLA B27 status ($n = 3$), BASDAI ($n = 1$), BASFI ($n = 1$), ASDAS-CRP ($n = 1$), PGA ($n = 1$), pain score ($n = 1$) and ASAS positive MRI ($n = 5$). ASDAS: Ankylosing Spondylitis Disease Activity Score; ASAS: Assessment of SpondyloArthritis international Society; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; bDMARD: biological disease modifying anti-rheumatic drugs; csDMARD: conventional synthetic disease modifying anti-rheumatic drugs; IQR: inter-quartile range; PGA: patient global assessment; PhGA: physician global assessment; SIJ: sacroiliac joints. Bold type indicates significance.

In cluster B, the 'High' and the 'Low' trajectory represented, respectively, 9 (38%) and 15 (62%) of 24 patients (Fig. 2). Similarly to cluster A, patients in the 'High' and 'Low' trajectory differed in baseline disease activity [ASDAS-CRP 3.6 (1.2) *vs* 2.8 (1.3), $P = 0.08$], which showed minor improvement in the 'High' trajectory but remarkably decreased in the 'Low' trajectory. Patients in the former group were older, less frequently male and more often had elevated CRP (Table 2). Male sex (OR = 0.2, 95% CI: 0.1, 0.6) and elevated CRP (OR = 5.8, 95% CI: 2.2, 15.5) remained independently associated with the 'High' trajectory after multivariate adjustment. In the 'High' and the 'Low' trajectory, patterns of PGA, pain and function scores were fluctuating over time respectively comparable to ASDAS-CRP (Supplementary Fig. S2, available at *Rheumatology* online).

Discussion

This prospective study is the first to comprehensively describe the prevalence, clinical patterns and prognostic implications of peripheral manifestations across the entire SpA spectrum. It benefited from the unique design of the Be-Giant cohort: longitudinal observation of well-characterized, newly diagnosed SpA patients, irrespective of the predominant symptom or symptom duration. Our study emphasized a marked heterogeneity within SpA, identifying two phenotypical clusters at the initial diagnosis with differential responses in longitudinal follow-up. In particular, peripheral manifestations add to the disease burden and appear to be a poor prognostic factor in axSpA.

In the Be-Giant cohort, documented peripheral manifestations were present in 44% of patients at or prior to diagnosis while 30% fulfilled the ASAS pSpA criteria. A similar pSpA proportion was found in the ESPeranza cohort (23%), one of the few cohort studies that equally included early axSpA and pSpA patients [15]. In Be-Giant patients classified as axSpA, only 20% had peripheral manifestations: 15% arthritis, 9% enthesitis and 2% dactylitis. These rates are comparable to the SPACE cohort but largely deviate from the GESPIC cohort (18–41% peripheral arthritis, 25–44% enthesitis and 3–4% dactylitis in recent onset non-radiographic axSpA) [16, 17] and the DESIR cohort (55% arthritis—including arthralgia—and 48% enthesiopathy in patients with early IBP classified as axSpA) [18]. The wide range of estimates regarding peripheral involvement in axSpA may have several reasons, besides the intrinsic differences in design between the aforementioned cohorts. First and foremost, various definitions of arthritis and enthesitis and possible incorrect patient recall of past symptoms complicate comparison. In this respect, the Be-Giant investigators adopted stringent criteria to prevent overdiagnosis, i.e. excluding arthralgia without evidence of joint swelling/inflammation and tender entheseal sites without (imaging) evidence of true enthesitis. This ambiguity does not apply to dactylitis, which is generally a clear clinical feature. Alternatively, a varying prevalence of peripheral manifestations may be attributed to different genetic susceptibility accounting for geographical variation [19]. This hypothesis is, however, unlikely because most studies report on Caucasian populations in Europe. Finally, peripheral involvement may be limited in Be-Giant axSpA patients because of their early disease stage (median symptom duration of 27 months). These patients might have had less time to accumulate peripheral manifestations. However, studies comparing early and advanced axSpA did not reveal a significant increase of peripheral manifestations in more long-standing disease [20, 21].

Through the use of cluster analysis on baseline patient characteristics, we identified two major SpA phenotypes with a predominant axial (cluster A) respectively peripheral clinical profile (cluster B). Patients with a mixed phenotype (axial and peripheral disease) generally shared more clinical features with patients in cluster A compared with cluster B, and thus did not segregate from the pure axSpA patients at baseline. While these results independently confirm the binary classification proposed by ASAS, they contrast to previous findings. In particular, a separate cluster enriched in peripheral manifestations was identified in a subset of IBP patients suspect for axSpA (DESIR cohort) as well as in a recent-onset chronic back pain cohort (SPACE) [22, 23]. These apparent differences may be due to distinct cohort entry criteria or the strikingly lower proportion of peripheral disease in Be-Giant patients classified as axSpA. In line with previous reports, peripheral involvement adds to the disease burden, with phenotypes or clusters involving peripheral manifestations showing higher disease activity compared with pure axSpA [5, 22, 24].

Analysis of disease activity patterns additionally revealed important differences in long-term outcomes within and between the clinical clusters identified at baseline. In the axial predominant cluster (A), 62% of patients followed a trajectory towards low disease activity ('Low' trajectory), which is consistent with other studies reporting on usual care [25]. More importantly, peripheral manifestations were independently associated with persistent high disease activity ('High' trajectory), even though bDMARDs—the vast majority being TNFi—were initiated twice as quickly in these patients compared with those with pure axial disease. In other words, despite more prompt therapeutic intensifications in SpA patients with a mixed phenotype, clinically defined as axial and peripheral disease, they do not respond accordingly. These clinical observations advocate strongly for the presence of a distinct SpA endotype, based on potentially different immunopathological mechanisms and characterized by high disease activity at initial presentation with lack of substantial improvement upon follow-up. Accordingly, one may question the need for other therapeutic strategies (i.e. bDMARDs with distinct modes of action) in this specific endotype. Its aberrant longitudinal behaviour is probably insufficiently recognized today because of baseline similarities with pure axSpA, as demonstrated in the cluster analysis.

In addition to this, patients in the peripheral predominant cluster (B) also showed differential responses during follow-up. Higher baseline disease activity proved to be a common feature in 'High' trajectory patients from both clusters, independently driven by peripheral disease in cluster A and elevated CRP in cluster B [26]. Moreover, male sex was identified as a predictor for a more favorable outcome in both clusters, consistent with previous findings [27].

Our study has several strengths. First, the Be-Giant consortium adopted broad but clearly defined inclusion criteria, resulting in a well-characterized patient cohort that covers the entire SpA spectrum. Second, the set-up closely reflected daily clinical practice because patients were included from the diagnosis onwards and therapeutic interventions were left at the discretion of the treating rheumatologist. Third, enrolment in geographically spread academic and peripheral outpatient clinics adequately represented the SpA population in our country.

A limitation to this study would be the exclusion of patients who were not adherent to follow-up, reducing the sample size in the longitudinal analysis. Although sensitivity analysis did not suggest major baseline differences between patients with complete or incomplete follow-up, our main results indeed indicate a potential different trajectory of patient populations with similar baseline profiles. In fact, patients' non-adherence also mirrors follow-up in routine clinical practice.

In conclusion, almost half of the newly diagnosed Be-Giant patients presented with peripheral manifestations, which determined baseline phenotypes and long-term outcomes. Stratification of axial predominant patients according to peripheral involvement permits the identification of an endotype with an unfavourable outcome after two-year follow-up, emphasizing its prognostic value as well as the need for an endotype-tailored rather than an ASDAS-driven therapeutic approach.

Acknowledgements

We thank the study participants, rheumatology and research nurses, and clinicians who have contributed to this study. A-S.DC., F.C., M-A.DA., F.VdB. and D.E. conceptualized and designed the study. A-S.DC., T.R., L.D., L.VP., H.C., G.V., R.J., M.D., L.G., I.P., K.T., J.L., P.C. and F.VdB. collected original clinical data. A-S.DC. performed statistical analysis and prepared the manuscript. A-S.DC., T.R., L.D., F.C., M-A.DA., P.C., F.VdB. and D.E. contributed to the analysis and the interpretation of the data. A-S.DC., F.VdB. and D.E. have verified the underlying data. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript for publication.

Funding: The Be-Giant cohort received an unrestricted grant from AbbVie. These financial resources have been used to support data collection and management. AbbVie had no role in study conception and design, data analysis and interpretation, or writing of this manuscript. The principal investigator and his team have full academic freedom and are able to work independently of pharmaceutical industry influence. The principal investigator and his team autonomously decided on data analyses and interpretation, writing of the manuscript, and publication, independent from any industrial contribution or other funding source. The corresponding author has full access to all the data in the study and takes the final responsibility for the decision to submit for publication.

Disclosure statement: A-S.DC., T.R., L.D., L. VP., H.C., G.V., R.J., M.D., L.G., I.P., K.T., J.L. and P.C. have nothing to disclose. F.C. reports personal fees from Lilly, UCB and Novartis, outside the submitted work. M-A.DA. reports personal fees from AbbVie, BMS, Novartis, Celgene, Janssen and grants from Pfizer, outside the submitted work. F.VdB. reports grants from AbbVie during the conduct of the study; personal fees from Abbvie, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer and UCB, outside the submitted work. D.E. reports grants from AbbVie during the conduct of the study; personal fees from Abbvie, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer and UCB, outside the submitted work.

Data availability statement

De-identified individual participants' data that underlie the results reported in this article, are available for researchers who provide a methodologically sound proposal. Data are available immediately following publication up to 5 years after publication. Data may be requested to achieve aims of the approved research proposal or for individual participant data meta-analysis. Proposals should be directed to dirk.elewaut@ugent.be; to gain access, data requestors will need to sign a data access agreement. For any further information, please contact the corresponding author: dirk.elewaut@ugent.be.

Supplementary data

Supplementary data are available at *Rheumatology* online.

References

1 Garrido-Cumbrera M, Poddubnyy D, Gossec L *et al.* The European map of axial spondyloarthritis: capturing the patient perspective-an analysis of 2846 patients across 13 countries. Curr Rheumatol Rep 2019;21:19.

2 Dougados M, Baeten D. Spondyloarthritis. Lancet 2011; 377:2127–37.

3 Rudwaleit M, Van Der Heijde D, Landewé R *et al.* The development of Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.

4 Rudwaleit M, van der Heijde D, Landewe R *et al.* The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and

for spondyloarthritis in general. Ann Rheum Dis 2011;70:25–31.

5 de Winter JJ, Paramarta JE, de Jong HM, van de Sande MG, Baeten DL. Peripheral disease contributes significantly to the level of disease activity in axial spondyloarthritis. RMD Open 2019;5:e000802.

6 Taylor W, Gladman D, Helliwell P *et al.* Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.

7 Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A *et al.* Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis 2003;62:127–32.

8 Lukas C, Landewe R, Sieper J *et al.* Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:18–24.

9 Machado PM, Landewe R, Heijde DV. Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. Ann Rheum Dis 2018;77:1539–40.

10 van der Heijde D, Lie E, Kvien TK *et al.* ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68:1811–8.

11 Yuan C, Yang H. Research on K-value selection method of K-means clustering algorithm. J Multidiscipl Sci J 2019;2:226–35.

12 Hennig C. Cluster-wise assessment of cluster stability. Comput Stat Data Anal 2007;52:258–71.

13 Magidson J, Vermunt J. Latent class models for clustering: comparison with K-means. Can J Market Res 2002;20:36–43.

14 Proust-Lima C, Philipps V, Liquet B. Estimation of extended mixed models using latent classes and latent processes: The R Package lcmm. J Statistical Software 2017;78:56.

15 del Rio-Martinez P, Navarro-Compan V, Diaz-Miguel C *et al.* Similarities and differences between patients fulfilling axial and peripheral ASAS criteria for spondyloarthritis: results from the Esperanza Cohort. Semin Arthritis Rheum 2016;45:400–3.

16 van den Berg R, de Hooge M, van Gaalen F *et al.* Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. Rheumatology 2015;54:1336.

17 Rudwaleit M, Haibel H, Baraliakos X *et al.* The early disease stage in axial spondylarthritis: results from the german spondyloarthritis inception cohort. Arthritis Rheum 2009;60:717–27.

18 Dougados M, d'Agostino MA, Benessiano J *et al.* The DESIR cohort: a 10-year follow-up of early inflammatory back pain in France: study design and baseline characteristics of the 708 recruited patients. Joint Bone Spine 2011;78:598–603.

19 Londono J, Santos AM, Peña P *et al.* Analysis of HLA-B15 and HLA-B27 in spondyloarthritis with peripheral and axial clinical patterns. BMJ Open 2015;5:e009092.

20 de Winter JJ, van Mens LJ, van der Heijde D, Landewé R, Baeten DL. Prevalence of peripheral and extra-articular disease in ankylosing spondylitis versus non-radiographic axial spondyloarthritis: a meta-analysis. Arthritis Res Ther 2016;18:196.

21 López-Medina C, Ramiro S, van der Heijde D *et al.* Characteristics and burden of disease in patients with radiographic and non-radiographic axial Spondyloarthritis: a comparison by systematic literature review and meta-analysis. RMD Open 2019;5:e001108.

22 Costantino F, Aegerter P, Dougados M, Breban M, D'Agostino MA. Two phenotypes are identified by cluster analysis in early inflammatory back pain suggestive of spondyloarthritis: results from the DESIR cohort. Arthritis Rheumatol 2016;68:1660–8.

23 Sepriano A, Ramiro S, van der Heijde D *et al.* What is axial spondyloarthritis? A latent class and transition analysis in the SPACE and DESIR cohorts. Ann Rheum Dis 2020;79:324–31.

24 López-Medina C, Moltó A, Dougados M. peripheral manifestations in spondyloarthritis and their effect: an ancillary analysis of the ASAS-COMOSPA Study. J Rheumatol 2020;47:211–7.

25 Molto A, López-Medina C, Van den Bosch FE *et al.* Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. Ann Rheum Dis 2021;80:1436–44.

26 Haroon M, Gallaghar P, Ahmad M, FitzGerald O. Elevated CRP even at the first visit to a rheumatologist is associated with long-term poor outcomes in patients with psoriatic arthritis. Clin Rheumatol 2020;39:2951–61.

27 Molto A, Tezenas du Montcel S, Wendling D *et al.* Disease activity trajectories in early axial spondyloarthritis: results from the DESIR cohort. Ann Rheum Dis 2017;76:1036–41.