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Clinical science

ANA-associated arthritis: clinical and biomarker characterization of a population for basket trials

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Abstract

Objectives: ANA-associated rheumatic and musculoskeletal (MSK) diseases (RMDs) [SLE, primary SS (pSS), scleroderma, inflammatory myositis, MCTD and UCTD] make up a disease spectrum with overlapping clinical and immunological features. MSK inflammation is common and impactful across ANA-associated RMDs. The objectives of this study were to evaluate MSK inflammation (ANA-associated arthritis) prevalence in a multidisease ANA-associated RMD study, assess its clinical impact across ANA-associated RMD diagnoses, propose new basket groupings of patients, and evaluate immunological profiles in legacy and new basket contexts.

Methods: An observational study enrolled patients with ANA-associated RMDs. Demographic variables, comorbidities, therapies, disease activity instruments [BILAG, SLEDAI, the EULAR SS disease activity index (ESSDAI), physician visual analogue scale (VAS)], patient-reported outcomes [SF36, FACIT-Fatigue, EQ5D, ICECAP-A, Work Productivity and Activity impairment (WPAI), patient VAS] and the biomarker profile (six-gene expression scores, flow cytometry, autoantibody profile) were analysed. Reclustering utilized Gaussian mixture modelling (GMM). The clinical and immune features of new and legacy clusters were compared.

Results: Inflammatory MSK symptoms were prevalent across ANA-associated RMDs, in 213/294 patients. In ANA-associated arthritis patients, most variables did not differ between diagnoses, with the exception of the EQ5D-5L index and mobility domains (lower in MCTD/pSS, both $P < 0.05$). FM and OA prevalence were similar across diagnoses. Therapy use differed significantly, the use of biologics being greatest in SLE ($P < 0.05$). GMM yielded two multidisease clusters: High MSK disease activity ($n = 89$) and low MSK disease activity ($n = 124$). The high MSK disease activity cluster included all patients with active joint swelling, and they had significantly higher prednisolone usage, physician global assessment (PGA), Sm/RNP/SmRNP/chromatin positivity, Tetherin mean fluorescence intensity (MFI), and IFN Score-A activity, along with numerically lower FM and OA prevalence.

Conclusion: We defined ANA-associated arthritis, a more clinically and immunologically homogeneous population than existing RMD populations for trials, and a more prevalent population for therapies in the clinic.

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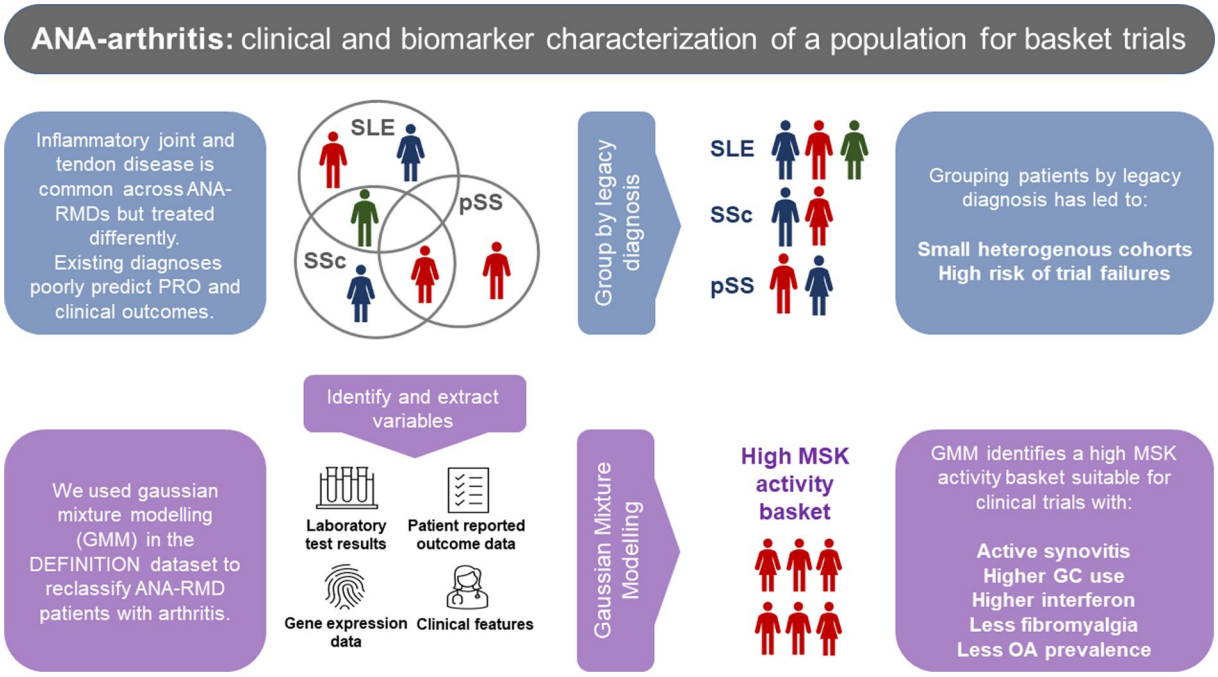
Graphical abstract



Keywords: arthritis, autoimmune diseases, SLE, Sjögren's syndrome, myositis.

Rheumatology key messages

- Arthritis is common in each ANA-associated RMD but is treated differently, according to disease-specific therapy and treatment guidelines.
- ANA-associated arthritis has a similar impact on patient- and physician-reported outcomes across ANA-associated RMDs.
- We define a more prevalent, active, clinically and immunologically homogenous ANA-associated arthritis population than the populations currently studied in clinical trials.

Introduction

ANA-associated rheumatic and musculoskeletal (MSK) diseases (RMDs) (ANA-associated RMDs) are a spectrum of overlapping diseases characterized by autoreactivity to nuclear antigens, encompassing SLE, primary SS (pSS), idiopathic inflammatory myopathies (IIMs) and SSc. Many patients have overlap syndromes, meeting classification criteria for multiple diseases, or undifferentiated forms of ANA-associated RMDs (UCTDs) that are not easily classified [1–3]. Despite distinct clinicopathological manifestations, such as specific antibodies, or skin fibrosis in SSc *vs* exocrine gland inflammation in pSS, ANA-associated RMDs also share features such as arthritis and immunopathogenic signatures [4–11].

Despite these shared features, treatment inequity exists between SLE and other ANA-RMDs. In SLE patients with arthritis, two targeted therapies are licensed, whereas there are none for patients with pSS with arthritis [12, 13]. Additionally, UCTD patients lack evidence-based treatment strategies and are ineligible for clinical trials. In single diseases such as SLE, diverse clinical and immunological presentations, such as cutaneous and MSK symptoms, pose challenges in defining trial populations, measuring outcomes, and assessing treatment effectiveness [14, 15]. Heterogeneity within SLE may partially explain how, despite encouraging clinical responses for certain disease manifestations, in several studies patients failed to meet multisystem primary end points, leading to programme discontinuation [12].

Reclassifying ANA-associated RMD patients into alternative 'baskets' may address these issues, as exemplified by approaches to autoimmune disease-associated interstitial lung disease [16]. Baskets may be defined as groups of patients from different legacy diagnoses who are suitable for a similar therapeutic intervention. Baskets may be based on shared pathogenic mechanisms (e.g. B-cell or Type-I IFN pathway activation) or a shared clinical problem (e.g. arthritis). Conducting clinical trials in a well-defined basket cohort could address unmet clinical needs and yield evidence-based interventions for patients across a wider spectrum of diagnoses. Furthermore, basket population trials may bolster effect sizes by utilizing more homogeneous study populations than existing trials, which cover multiple organ manifestations, biomarker subgroups, and background therapeutics. ANA-associated RMD arthritis may be a suitable basket for this strategy as it is common and significantly impacts quality of life, functional disability, work impairment, and health/economic outcomes [17, 18].

The study objectives were: (i) to evaluate the prevalence of 'ANA-associated arthritis', defined as synovitis, tenosynovitis, enthesitis or other articular/peri-articular inflammation in patients with ANA-associated RMD, in a multidisease study; (ii) to test the hypothesis that ANA-associated arthritis has a similar clinical impact across legacy diagnoses; (iii) to define new basket groupings of patients across the ANA-associated RMD spectrum for clinical trials; (iv) to evaluate immunological profile, and therefore suitability for therapies, of legacy diagnoses and new therapeutic baskets.

Methods

The DEFINITION cohort

The patient recruitment, variables collected, and use in statistical analyses are summarized in Fig. 1. Research ethics approval was obtained from the UK Health Research Authority (IRAS ref. 60762]. Written informed consent was obtained from all patients.

DEFINITION is a prospective, multidisease ANA-associated RMD cohort study in Leeds, United Kingdom, since May 2017. The primary aims were to better define the role of IFN-I and other biomarkers in ANA-associated RMD and refine the use of IFN-I targeted, conventional and other therapies. This analysis focused on patients with a history of inflammatory arthritis or currently active disease. Patients were identified through US-documented synovitis at enrolment, the presence of inflammatory arthritis items on validated instruments [BILAG-2004 A-C articular/tendinopathy domains or ESSDAI (EULAR SS disease activity index)], or any of the following terms in their medical documentation: arthropathy; arthritis; arthralgia; synovitis; tenosynovitis; joint tenderness; epicondylitis; polyarthralgia. All individuals provided informed written consent, and this research was carried out in compliance with the Declaration of Helsinki. This study was approved by the National Health Service Health Research Authority (REC Ref: 17/YH/0166). Healthy control participants' peripheral blood was collected under study number 04/Q1206/107. All experiments were performed in accordance with relevant guidelines and

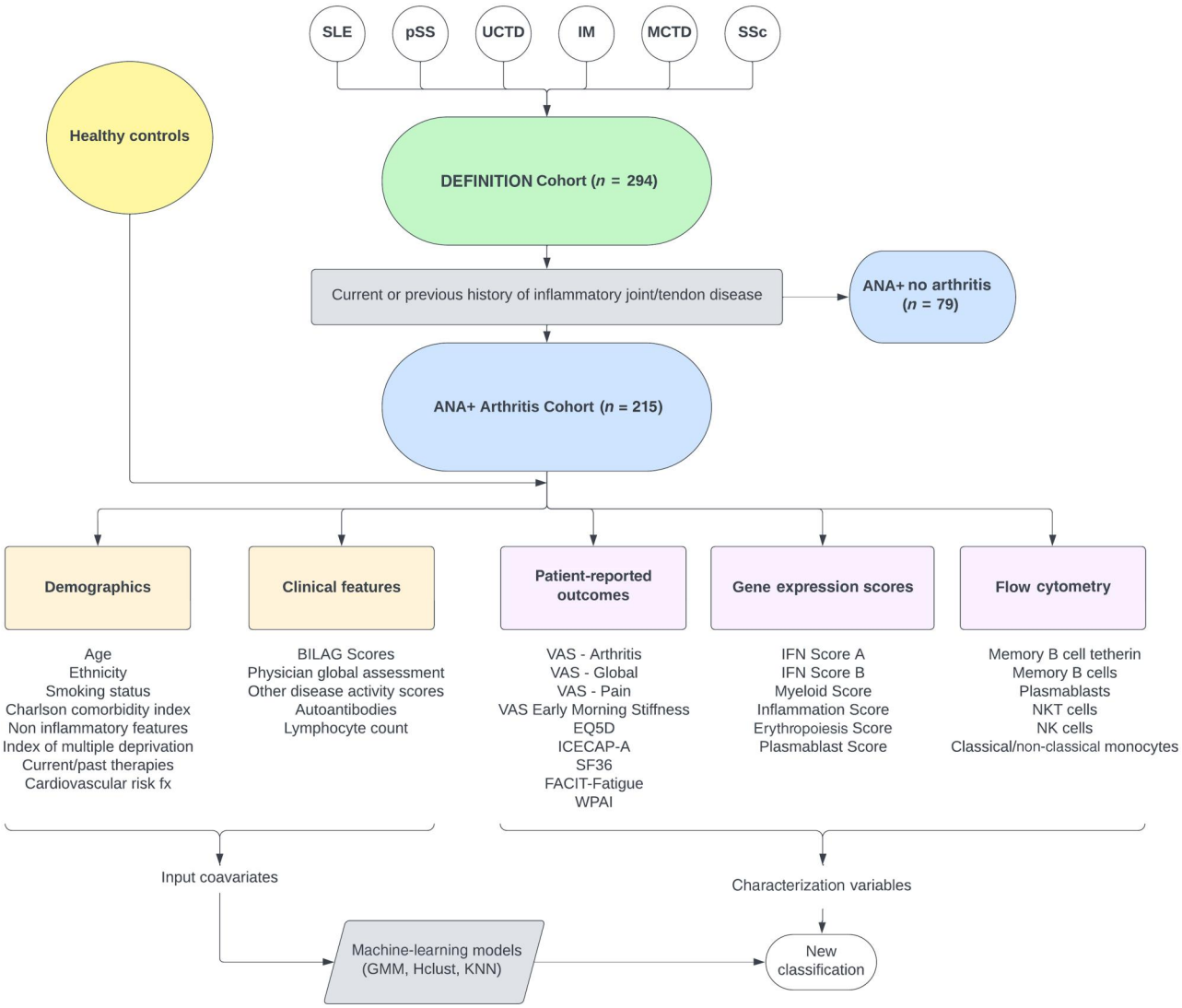


Figure 1. Study schematic. pSS: primary SS; IM: idiopathic myositis; WPAI: Work Productivity and Activity impairment; NKT: NK T cell

regulations. The University of Leeds was contracted with administrative sponsorship.

Demographics and comorbidity

We collected baseline age, gender, patient-identified ancestry, smoking status, index of multiple deprivation (IMD) [19], Charlson comorbidity index (CCI) [20], clinical features of FM, hypermobility and OA. Diagnoses were recorded according to consultant physician review. This was preferred over diagnostic criteria, which are absent in UCTD and often unfulfilled in pSS without tissue biopsy.

Laboratory measures

Full blood count, complement C3 and C4 levels and ANA subtypes, including anti-dsDNA, Ro-52, Ro-60, La, Sm, SM/RNP, RNP, Scl-70, Jo-1, Centromere, Chromatin and Ribosomal-P antibodies (Bioplex multiplex analyser) were measured in a routine diagnostic laboratory. Peripheral blood mononuclear cell (PBMC) subsets were analysed using 8-colour flow cytometry as a proportion of total PBMC count [T cells (CD3 + CD56−), NK-cells (CD56+), NKT-cells (CD3 + CD56+), Memory B-cells (CD19+ CD27+), Plasmablasts (CD19±CD27 + CD38++), classical monocytes (CD14 ++ CD16−) intermediate monocytes (CD14++CD16+) and non-classical monocytes (CD14 + CD16+)]. Tetherin (CD317) mean fluorescence intensity was quantified on each cell subset, with memory B cell level as the primary biomarker [21].

Two validated IFN-stimulated gene expression scores (IFN Score-A and IFN Score-B) were analysed. PBMCs were separated using the density gradient method (Lymphoprep; Alere-Technologies, Oslo, Norway) from EDTA-anticoagulated blood. A total RNA purification kit (Norgen-Biotek, Thorold, Canada) was used followed by quantitative real-time reverse transcriptase-PCR (qRT-PCR) using TaqMan assays (Applied Biosystems, Invitrogen) for the selected 30 Interferon-stimulated genes (ISGs) as previously described [22, 23]. Scores for genes annotated to plasmablast, myeloid lineage, inflammation and erythropoiesis function were included from previously described modules, based on their known molecular function [24]. We used untransformed dCT gene expression scores to preserve a normal distribution. For untransformed values in the figures and tables, numerically lower dCT values represent higher gene expression.

Clinical assessment

Disease activity was assessed at baseline using validated instruments applied to all diagnostic groups: ESSDAI; BILAG 2004 index; SLEDAI-2K. Rodnan skin score and MITAX were collected but not analysed due to limited relevance to clinical features and patient numbers. Physician global assessment (PGA) was also assessed. The validity of the articular component of the BILAG-MSK domain (excluding myositis) across non-SLE diagnoses was explored using association with PGA.

Patient-reported outcomes

Patient-reported disease impact was assessed using the following: 36-item Short Form Survey (SF36)—Composite and domain scores; Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-Fatigue); EuroQol-5 Dimension 5-level Score (EQ5D-5L)—Index and domain scores; ICECAP-A; Patient-reported visual analogue scales (VASs); Arthritis-VAS; Pain-VAS; Global-VAS; Fatigue-VAS; Global health-VAS and Early Morning Stiffness-VAS.

Machine learning

Model covariates were selected based on background evidence (MSK-BILAG Sm/SmRNP/RNP antibody status) and principle component analysis (PCA). PCA of 40 covariates, including age, IMD-rank, prednisolone dosage, 15 extractable nuclear antigen (ENA) values, PGA, numeric MSK-BILAG, 8-gene expression scores, 6 flow cytometry subsets, and 6 non-inflammatory features, identified 7 covariates for GMM. The primary variance was explained by IMD-rank, prednisolone dosage, numeric MSK-BILAG score, lymphocyte count, chromatin antibody positivity, Ro52/Ro60 antibody positivity, and Sm/SmRNP/RNP antibody positivity. Selected values explained >99.99% of data variance in the first 3 principal components within the 7-covariate model through singular value decomposition.

Multiple imputation with chained equations (MICE) was utilized to address missingness, with 3.75% ($n = 8$) of the IMD-rank data and 8.92% ($n = 19$) of the lymphocyte count values being imputed. Hierarchical clustering, k-means clustering, and GMM were trialled using the hclust and base-R packages.

Statistical analysis

Statistical analysis and data visualization utilized the heatmap, corrplot, ggplot and tableone packages in R version 4.1.2. Multiple group comparison employed Kruskal–Wallis testing, while twin group comparisons of categorical and continuous variables utilized χ^2 and T-tests, respectively. For correlation analyses, Spearman's rank correlation coefficient was used, considering correlations ≥ 0.3 or ≥ -0.3 as substantive. Bonferroni correction was applied to compensate for multiple-hypothesis testing. PCA and GMM utilized the Mclust v6.0.0 packages. Data imputation used the MICE v3.15.0 package. Sankey plots were generated using SankeyMatic.

Patient and public involvement

The NIHR Leeds Biomedical Research Centre patient and public involvement (PPI) group have regular insight and input into planning and conduct of local ANA-associated RMD research. A workshop held when designing the study identified arthritis as a key problem of interest.

Results

Prevalence of inflammatory joint and tendon disease in ANA-associated RMDs

Of 294 patients with ANA-associated RMDs recruited to DEFINITION, 213 with inflammatory articular features were included. The key baseline features are detailed in Table 1. The SSc and pSS groups had a higher median age and were more comorbid than other ANA-associated RMDs with a higher baseline CCI ($P = 0.021$ and 0.033, respectively). SLE and myositis groups had higher proportions on long-term prednisolone therapy. MSK inflammation was common, and most prevalent in SLE and MCTD patients (87% and 77%, respectively).

No significant differences were observed in physician-defined FM features among diagnostic groups. No significant differences were found in the prevalence of nodular OA (on

Table 1. Baseline characteristics of DEFINITION cohort

Variable	SLE	UCTD	pSS	MCTD	IM	SSc	*P*
Total, *n*	104	111	33	13	19	14	
MSK inflammation, *n*	90	77	23	10	6	7	
MSK inflammation, %	87%	69%	70%	77%	32%	50%	
Sex = M (%)	10 (11.1)	10 (13.0)	1 (4.3)	1 (10.0)	2 (33.3)	2 (28.6)	0.33
Age, mean (S.D.), years	46.20 (14.22)	50.17 (12.93)	55.96 (13.93)	48.60 (12.66)	50.17 (20.44)	59.29 (15.22)	0.021
Ancestry, *n* (%)							
Other/unknown	8 (8.9)	10 (13.0)	3 (13.0)	1 (10.0)	1 (16.7)	0 (0.0)	
Asian	14 (15.6)	8 (10.4)	2 (8.7)	1 (10.0)	0 (0.0)	1 (14.3)	
Mixed	4 (4.4)	2 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	
European	57 (63.3)	51 (66.0)	18 (78.3)	8 (80.0)	4 (66.7)	5 (71.4)	
African	7 (7.8)	6 (7.8)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	
Current smoker (%)	10 (11.1)	8 (10.4)	0 (0.0)	2 (20.0)	1 (16.7)	0 (0.0)	0.424
IMD rank [mean (S.D.)]	12 998 (10 263)	15 767 (10 511)	18 573 (9456)	15 709 (9346)	17 691 (13 968)	9890 (11 320)	0.14
CCI total [mean (S.D.)[	2.00 (1.38)	2.04 (1.34)	2.91 (1.47)	2.10 (1.97)	1.67 (1.21)	3.29 (2.87)	0.033
FMS pain/stiffness (%)	19 (21.1)	10 (13.0)	3 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.221
FMS allodynia (%)	9 (10.0)	5 (6.5)	1 (4.3)	0 (0.0)	0 (0.0)	1 (14.3)	0.698
Hypermobility syndrome (%)	3 (3.3)	3 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.883
Nodal OA (%)	6 (6.7)	4 (5.2)	3 (13.0)	1 (10.0)	1 (16.7)	2 (28.6)	0.257
X-ray-proven OA (%)	11 (12.2)	13 (16.9)	4 (17.4)	2 (20.0)	1 (16.7)	2 (28.6)	0.851
Lymphocyte count $\times 10^9$/l [mean (S.D.)]	1.27 (0.59)	1.53 (0.73)	1.43 (0.65)	1.13 (0.64)	1.15 (0.70)	1.32 (0.31)	0.153
BILAG numeric [mean (S.D.)]	4.96 (6.01)	3.09 (4.45)	2.83 (2.81)	5.80 (5.73)	5.50 (7.18)	4.86 (4.38)	0.14
ESSDAI total [mean (SD)]	2.46 (3.54)	1.86 (3.58)	2.52 (3.49)	3.90 (5.36)	1.67 (2.34)	0.71 (1.50)	0.429
SLEDAI total [mean (SD)]	5.60 (4.10)	3.19 (1.82)	2.83 (2.15)	6.00 (4.97)	5.33 (4.13)	2.86 (1.57)	<0.001
PGA Q2 [mean (S.D.)]	2.84 (2.17)	2.49 (1.88)	2.86 (1.81)	4.05 (2.36)	4.37 (3.87)	3.77 (1.91)	0.087

Musculoskeletal (MSK) inflammation was defined as current/previous active MSK disease as defined by the BILAG-2004 and ESSDAI criteria or any documentation of joint or tendon inflammation within the medical notes. *P* values refer to the Bonferroni-corrected ANOVA for continuous variables and the Chi squared test for categorical variables. CCI: Charlson comorbidity index; ESSDAI: EULAR SS disease activity index; FMS: FM syndrome; IMD: index of multiple deprivation; PGA: physician global assessment.

clinical examination), X-ray-confirmed OA, or hypermobility syndrome.

Validity of MSK-BILAG across ANA-associated RMDs

To compare disease activity across ANA-associated RMDs, we explored the concurrent validity of articular scores within the MSK component of the BILAG-2004 Index. This demonstrated face validity across all RMDs, relying on the presence of inflammatory pain or swelling to categorize arthritis/tenosynovitis severity. Its definition mirrors the articular MSK assessment in MITAX and ESSDAI, each encompassing mild, moderate and severe grades for MSK inflammation. BILAG-2004 articular MSK grades A–D were significantly associated with PGA across both SLE ($F = 14.43$, $P < 0.001$) and non-SLE patients ($F = 11.62$, $P < 0.001$), supporting the use of this measure in classifying arthritis patients with various ANA-associated RMDs, pending further validation.

Clinical impact of joint and tendon inflammation in ANA-associated RMDs

To compare the clinical impact of articular symptoms across ANA-associated RMDs, we assessed physician-reported outcomes. Numeric BILAG-2004 values, ESSDAI total, and physician global assessment did not differ significantly between diagnoses (Table 1). Overall disease activity, as per the BILAG score and individual domains, did not significantly differ across groups except for BILAG gastrointestinal domain activity, which was highest in SLE ($P > 0.05$, Supplementary Table S1, available at *Rheumatology* online). SLEDAI-2K scores also differed significantly, being highest in the MCTD group ($P < 0.001$, Table 1).

We compared patient-reported outcomes for symptoms (pain-VAS, EMS-VAS, arthritis-VAS, fatigue-VAS and global health-VAS), quality of life (SF36-MCS, SF36-PCS, EQ5D-5L), participation (ICECAP-A) and fatigue (FACIT-Fatigue) across ANA-associated RMDs (Fig. 2).

Patients reported similar disease impact on their quality of life across all SF36 domains and 5 visual analogue scores (pain, early morning stiffness, arthritis, global health, and fatigue). There were numeric but non-significant differences in FACIT-Fatigue scores (highest in MCTD patients, $F = 1.767$, $P = 0.12$). Significant differences were observed in EQ5D-5L index scores between RMD groups ($F = 2.564$, $P = 0.03$), which were lowest in MCTD patients (0.43), and the EQ5D mobility domain ($F = 2.611$, $P = 0.03$), which was lowest in pSS patients.

We then assessed whether patient-reported impact was associated with disease activity (Supplementary Fig. S2, available at *Rheumatology* online). Patient-reported VAS scores for pain, arthritis and early morning stiffness correlated well with BILAG-MSK scores when comparing BILAG A/B and D/E disease ($P < 0.05$ in all). FACIT-fatigue scores also showed a significant correlation ($P < 0.05$). EQ5D and SF36 domain scores were not associated as tightly with articular MSK-BILAG scores, likely due to confounding in composite scoring tools covering several domains.

Current therapeutics in ANA-associated arthritis

We assessed whether the similar clinical and immunological features of ANA-associated arthritis across diagnoses were matched by therapeutic use. This significantly differed across diagnoses (Supplementary Table S3, available at *Rheumatology* online). Current and previous biologic use was significantly associated with diagnosis ($\chi^2 = 11.933$ and 12.335, respectively,

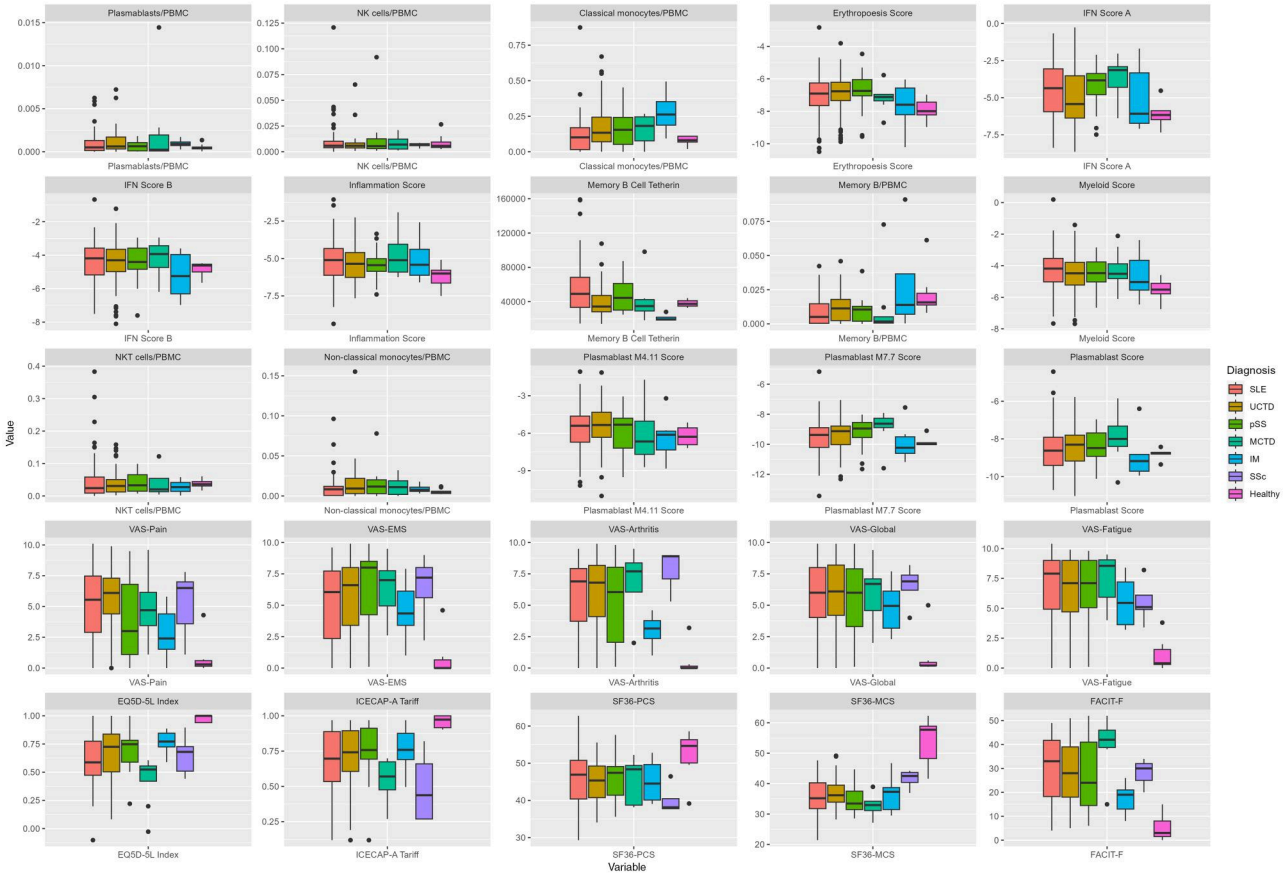


Figure 2. PRO and biomarker data by diagnosis. pSS: primary SS; IM: idiopathic myositis; PBMC: peripheral blood mononuclear cell; VAS: visual analogue score; EMS: early morning stiffness; PCS: physical component score; MCS: mental component score; pSS: primary SS

and $P < 0.05$ both). Biologic use was greater in the SLE group [18/90 (20%) previously received, 12/90 (13%) currently receiving] and MCTD group [3/10 (30%) previously received, 2/10 (20%) currently receiving] compared with other diagnoses [combined, 6/113 (5%) previously received, 5/113 (4%) currently received]. Previous AZA use was significantly greater in the SLE group, and current MMF use was greater in the SSc group ($P < 0.001$ in both). Among those currently on prednisolone, doses were notably higher in the IM group (7.83 mg, $P < 0.05$). These differences may reflect current guideline impact on practice, but may be unjustified given the relative homogeneity in immunological and patient-reported aspects across diagnoses.

Regarding therapeutic confounders, among the seven model covariates, only three exhibited significant associations: Chromatin antibody positivity correlated with higher HCQ use (27.0% *vs* 14.3%, $P = 0.04$), lower mean lymphocyte counts with increased AZA prescription (1.0 *vs* 1.42, $P = 0.01$), and current MMF treatment with higher previous rituximab therapy rates (34.6% *vs* 9.1%, $P < 0.01$) and lower mean IMD-rank (15582.72 *vs* 8990.35, $P < 0.01$).

Alternative predictors of disease outcomes

Statistical analysis with paired *t*-tests revealed several ENA subtypes linked to increased disease activity (defined by PGA). Sm, SmRNP and RNP antibody positivity were all associated with significantly higher PGA scores (*P*-values 0.016, 0.008, and 0.005, respectively; Supplementary Fig. S4, available at *Rheumatology* online).

Machine-learning reclassification of ANA-associated arthritis

Existing SLE trial designs recruit active disease within individual diagnoses. We estimated the proportion of patients with disease activity likely to be suitable for immunosuppressive therapy (BILAG A/B) among the 213 patients with MSK symptoms. We identified 16 patients (7.5%) with a diagnosis of SLE and BILAG-MSK A/B disease, and 30 patients (13.0%) had BILAG-MSK A/B disease irrespective of their diagnosis. These values indicate prevalent baskets of patients with active arthritis across the ANA-associated RMD spectrum, which we explored using machine learning.

GMM identified two clusters (Table 2). Kmeans and hierarchical clustering were also trialled but were poorer identifiers of high BILAG-MSK disease activity patients than GMM. Overall, cluster 1 contained more patients with inflammatory features (High MSK Activity Cluster; Cluster 1) and cluster 2 contained more patients with non-inflammatory causes of joint pain (Low MSK Activity Cluster; Cluster 2). Cluster 1 comprised 89 patients (41.8%), including all patients with BILAG A/B MSK disease. Cluster 1 patients were younger, with a lower proportion of UCTD and pSS. They included a higher proportion of SLE and MCTD patients, with a lower mean Charlson Comorbidity Index ($P = 0.002$). Cluster 1 contained substantively lower numbers of patients with nodal OA (3.4% for cluster 1 *vs* 11.3% for cluster 2, $P = 0.065$); radiographic evidence of OA (10.1% for cluster 1 *vs* 19.4% for cluster 2, $P = 0.10$); FM symptom pain and stiffness (9% for cluster 1 *vs* 19.4% for cluster 2, $P = 0.058$); and FM allodynia (3.4% *vs* 10.5%,

Table 2. Characteristics of ANA-associated RMD clusters

	GMM Cluster 1 High MSK activity $N = 89$	GMM Cluster 2 Low MSK activity $N = 124$	*P*-value
Demographics			
n	89	124	
Sex = M (%)	13 (14.6)	13 (10.5)	
Age [mean (s.d.)], years	44.28 (14.46)	53.01 (12.83)	
Diagnosis (%)			<0.001
SLE (*n*, % of cluster)	48 (53.9)	42 (33.9)	
UCTD	23 (25.8)	54 (43.5)	
pSS	3 (3.4)	20 (16.1)	
MCTD	9 (10.1)	1 (0.8)	
IIM	4 (4.5)	2 (1.6)	
SSc	2 (2.2)	5 (4.0)	
Other demographics			
Charlson comorbidity index [mean (s.d.)]	1.78 (1.16)	2.42 (1.65)	0.002
Non-inflammatory			
FMS pain/stiffness (%)	8 (9.0)	24 (19.4)	0.058
FMS allodynia (%)	3 (3.4)	13 (10.5)	0.093
Hypermobility syndrome (%)	2 (2.2)	4 (3.2)	0.995
Nodal OA (%)	3 (3.4)	14 (11.3)	0.065
X-ray- proven OA (%)	9 (10.1)	24 (19.4)	0.1
Current therapies			
Current prednisolone (%)	41 (97.6)	14 (11.3)	<0.001
Current prednisolone dose [mean (s.d.)]	5.53 (7.70)	0.58 (1.68)	<0.001
Current HCQ (%)	50 (56.2)	65 (52.4)	0.686
Current MTX (%)	18 (20.2)	25 (20.2)	1
Current MMF (%)	11 (12.4)	15 (12.1)	1
Current AZA (%)	9 (10.1)	12 (9.7)	1
Current RTX (%)	13 (14.6)	7 (5.6)	0.048
Previous therapies			
Previous AZA (%)	22 (24.7)	23 (18.5)	0.359
Previous HCQ (%)	15 (16.9)	25 (20.2)	0.666
Previous MTX (%)	20 (22.5)	19 (15.3)	0.25
Previous MMF (%)	17 (19.1)	11 (8.9)	0.048
Previous RTX (%)	14 (15.7)	12 (9.7)	0.263
Previous CYC (%)	10 (11.2)	14 (11.3)	1
Selected other clinical features (see supplement)			
RP (%)	32 (36.0)	18 (14.5)	0.001
Alopecia (%)	25 (28.1)	14 (11.3)	0.003
Immunology			
dsDNA (%)	27 (30.3)	35 (28.2)	0.856
Ro60 (%)	27 (30.3)	45 (36.3)	0.448
Ro52 (%)	23 (25.8)	27 (21.8)	0.598
La (%)	9 (10.1)	13 (10.5)	1
Sm (%)	20 (22.5)	0 (0.0)	<0.001
SmRNP (%)	33 (37.1)	0 (0.0)	<0.001
RNP (%)	19 (21.3)	0 (0.0)	<0.001
Chromatin (%)	45 (50.6)	0 (0.0)	<0.001
Clinical/Lab tests			
Lymphocyte count $\times 10^9$/l [mean (s.d.)]	1.30 (0.69)	1.44 (0.63)	0.133
BILAG Scores			
BILAG Numeric [mean (s.d.)]	6.62 (6.64)	2.30 (2.76)	<0.001
BILAG Total (%)			<0.001
A	28 (31.5)	4 (3.2)	
B	16 (18.0)	21 (16.9)	
C	41 (46.1)	82 (66.1)	
D/E	4 (4.5)	17 (13.7)	
BILAG Mucocutaneous (%)			0.1
A	4 (4.5)	3 (2.4)	
B	15 (16.9)	16 (12.9)	
C	15 (16.9)	10 (8.1)	
D/E	55 (61.8)	95 (76.6)	
BILAG MSK (%)			<0.001
A	22 (24.7)	0 (0.0)	
B	8 (9.0)	0 (0.0)	
C	44 (49.4)	91 (73.4)	
D/E	15 (16.9)	33 (26.6)	
BILAG General (%)			0.015
B	6 (6.7)	2 (1.6)	
C	5 (5.6)	1 (0.8)	
D/E	78 (87.6)	121 (97.6)	

(continued)

Table 2. (continued)

	GMM Cluster 1 High MSK activity $N = 89$	GMM Cluster 2 Low MSK activity $N = 124$	*P*-value
BILAG Haematological (%)			0.054
B	1 (1.1)	0 (0.0)	
C	29 (32.6)	25 (20.2)	
D/E	59 (66.3)	99 (79.8)	
BILAG Renal (%)			0.618
B	3 (3.4)	4 (3.2)	
C	2 (2.2)	6 (4.8)	
D/E	84 (94.4)	114 (91.9)	
Other physician disease activity measurements			
ESSDAI Total [mean (S.D.)]	3.79 (4.56)	1.12 (2.07)	<0.001
SLEDAI Total [mean (S.D.)]	5.81 (3.97)	3.31 (2.56)	<0.001
Physician global assessment [mean (S.D.)]	3.86 (2.39)	2.13 (1.55)	<0.001
Patient-reported outcome scores			
Pain VAS [mean (S.D.)]	5.40 (2.49)	4.90 (3.07)	0.261
EMS VAS [mean (S.D.)]	6.10 (2.65)	5.51 (3.01)	0.204
Arthritis VAS [mean (S.D.)]	5.85 (2.93)	5.89 (2.91)	0.945
Global VAS [mean (S.D.)]	5.79 (2.59)	5.61 (2.86)	0.675
Fatigue VAS [mean (S.D.)]	6.78 (2.62)	6.38 (3.08)	0.373
EQ5D-5L Index [mean (S.D.)]	0.63 (0.20)	0.65 (0.23)	0.509
EQ5D Self Care [mean (S.D.)]	1.99 (1.18)	1.69 (1.06)	0.079
ICECAP Total [mean (S.D.)]	0.70 (0.22)	0.68 (0.22)	0.432
SF36 Physical Component Score [mean (S.D.)]	45.64 (7.32)	45.09 (6.23)	0.653
SF36 Mental Component Score [mean (S.D.)]	36.44 (5.76)	36.15 (5.50)	0.778
FACIT Fatigue Total [mean (S.D.)]	30.19 (12.39)	28.18 (13.85)	0.365
Biomarkers			
Memory B cell Tetherin MFI [mean (S.D.)]	52882 (31936)	41979 (20287)	0.018
Interferon Score A dCt [mean (S.D.)]	4.33 (1.95)	4.92 (1.66)	0.021
Erythropoesis Score dCt [mean (S.D.)]	7.21 (1.38)	6.87 (1.19)	0.064
Inflammation Score dCt [mean (S.D.)]	5.15 (1.41)	5.29 (1.14)	0.453
Memory B cells/PBMCs [mean (S.D.)]	0.009 (0.01)	0.013 (0.01)	0.057

pSS: primary SS; ESSDAI: EULAR SS disease activity index; EMS: early morning stiffness; FMS: FM syndrome; IIM: idiopathic inflammatory myopathy; MSK: musculoskeletal; RMD: rheumatic and musculoskeletal disease; RTX: rituximab; VAS: visual analogue scale.

$P = 0.093$). RNP/SmRNP/Sm antibody positivity was significantly greater in cluster 1 patients. Numeric BILAG, ESSDAI, SLEDAI and physician global assessment scores were all significantly higher in cluster 1 patients ($P < 0.001$ in all). Memory B cell Tetherin and IFN score-A expression was also significantly higher in cluster 1 ($P = 0.018$ and $P = 0.021$; note that with untransformed gene expression scores, numerically lower values represent higher gene expression). Cluster 1 patients received more frequent and higher dose prednisolone. PCA plots formed from the seven GMM covariates are shown in Fig. 3.

Key potential confounders, including IMD rank, mucocutaneous, renal, neurological, and gastrointestinal BILAG scores, as well as Rodnan skin score, showed no significant differences between the GMM-derived clusters. Interestingly, Cluster 1 patients exhibited higher MSK disease activity, despite significantly higher rates of previous treatment with rituximab (14.6% *vs* 5.6%) and MMF (19.1% *vs* 8.9%) ($P < 0.05$ for both).

The distribution of patients between legacy diagnoses and new GMM clusters is shown in Fig. 4 to illustrate potential trial stratification strategies. Conventional trial designs recruit patients with SLE and swollen joints. After reclassification, the High MSK Activity Cluster (cluster 1) included all those patients as well as larger numbers from other RMDs. All patients in the High MSK Activity cluster with swollen joints would be eligible for an ANA-associated arthritis trial design and represent twice as many patients as a conventional SLE trial design. The remaining patients in the High MSK Activity Cluster lacked swollen joints at assessment but were similar in terms of immune biomarkers and clinical impact. These patients may be hypothesized to have a higher rate of joint inflammation when assessed over a longer time period, under different glucocorticoid or other immunosuppressive medications, or with MSK imaging, which has been shown to detect joint inflammation in a larger percentage of symptomatic populations [25]. Therefore, these patients in the High MSK Activity Cluster may be additional candidates for therapy licensed for ANA-associated arthritis in clinical practice.

Discussion

This is the first work assessing the clinical impact and immune profile of arthritis across multiple RMDs in a systematically collected, richly phenotyped, multidisease cohort. We demonstrate that ANA-positive RMD patients with MSK symptoms contain a High MSK Disease Activity population that is homogeneous in clinical features, patient-reported impact, and immune profile. The existing classification had previously distributed patients with ANA-associated arthritis into other groups based on their additional disease features, potentially resulting in unjustified variations in therapy. Instead, we suggest and define a novel classification that consolidates all patients with ANA-associated arthritis into a single group. This classification can facilitate basket trials, provide new therapy indications and inform routine clinical care guidelines.

We identified few differences between patients with MSK symptoms across RMD diagnoses, including physician- and

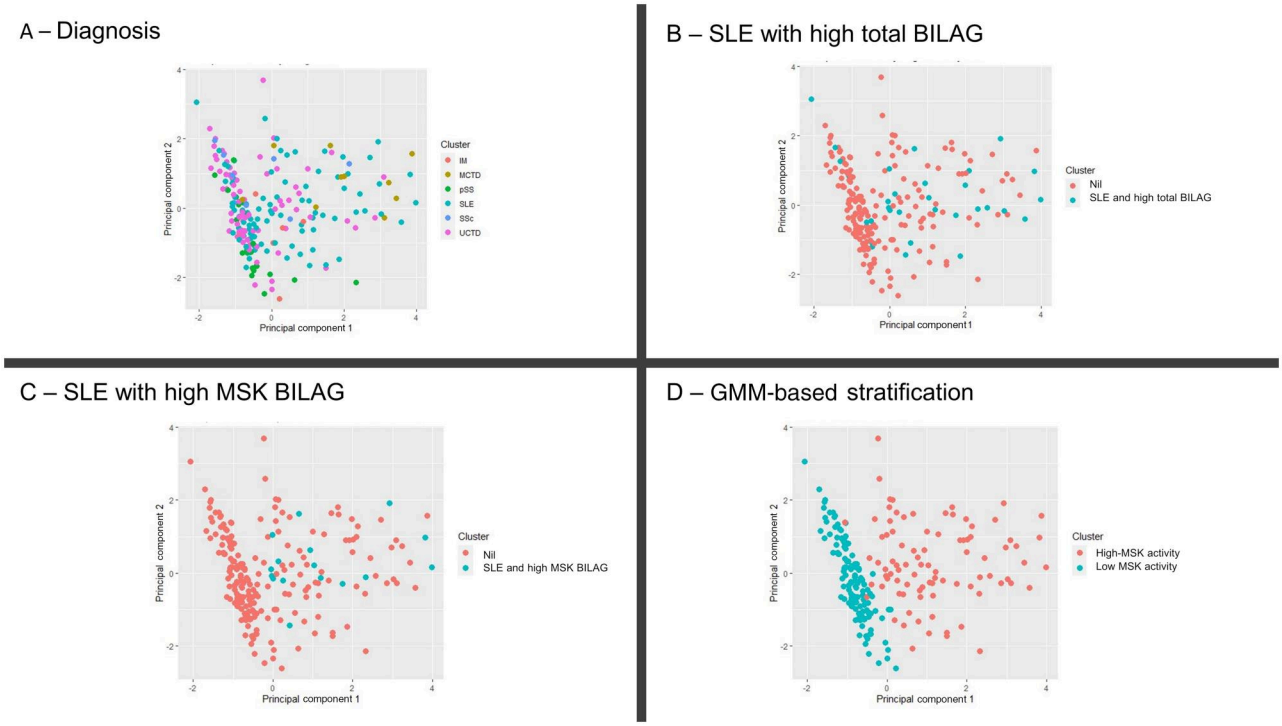


Figure 3. Collated PCA plots: (**A**) diagnosis; (**B**) SLE with high total BILAG; (**C**) SLE with high MSK BILAG; (**D**) GMM-based stratification. GMM: Gaussian mixture modelling; pSS: primary SS; IM: idiopathic myositis; MSK: musculoskeletal

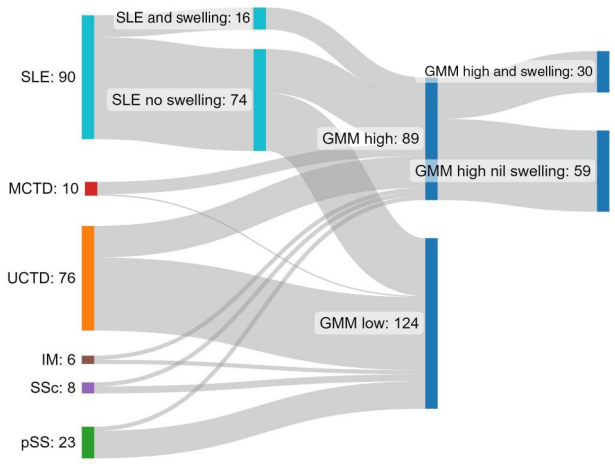


Figure 4. Sankey plot showing make-up of GMM high and low groups. GMM: Gaussian mixture modelling; pSS: primary SS; IM: idiopathic myositis

patient-reported clinical outcomes and biomarkers, with the exception that MCTD was generally worse. As expected from previous work, patients with MSK symptoms included a mixture of (i) patients with objective disease activity and (ii) patients with low disease activity and non-inflammatory explanations for pain, collectively, and for each legacy diagnosis.

During machine-learning (ML) analysis, patients with MSK symptoms were not sorted according to legacy diagnosis. Instead, the GMM approach generated High and Low MSK Disease Activity clusters, showing greater homogeneity compared with diagnoses such as SLE and UCTD. The High Disease Activity cluster included every patient with joint swelling, and other features such as higher physician global assessment, prednisolone dose, and IFN score. The Low Disease Activity cluster included more patients with features of FM and OA. Patient-reported outcomes such as pain, fatigue, and quality of life did not vary between clusters, as expected, given that both inflammatory and non-inflammatory causes of pain may equally affect patient experience. The High Disease Activity cluster included many patients without joint swelling, grouped together on the basis of other features, such as prednisolone dose, Sm, RNP, Sm/RNP, chromatin and Ro antibodies, lymphocyte count, and IMD rank. Although lacking documented joint swelling on the study visit day, these patients might exhibit joint inflammation on US imaging (as we previously demonstrated with the same antibody subtypes) or would present with joint swelling if the prednisolone dose were reduced or if assessed over a longer duration [25].

The High MSK Disease Activity group may be suitable for basket clinical trials. Current SLE clinical trials involve patients with diverse organ manifestations, requiring complex disease activity instruments for comparing the severity and response across various presenting complaints. Current SLE trials trials may also necessitate a variety of standard-of-care therapies. These factors may have contributed to inconsistent trial results [14, 15]. Conversely, clinical trials in ANA-associated arthritis would recruit a more homogeneous population, despite their inclusion of various legacy diagnoses. This enables the use of robust organ-specific outcome measures, such as the LAMDA, which combines swollen joint count, patient and physician VAS, and acute phase markers. In SLE, this principle is shown by a litifilimab phase-2 trial meeting its primary end point of joint counts, or baricitinib trials achieving MSK-specific secondary and exploratory variables [14, 26]. Multisystem disease activity tools would only be required to monitor for worsening in other organs. ANA-

associated arthritis trials could recruit more patients, and possibly incorporate MSK imaging. The resulting evidence base would be relevant to a larger patient population than SLE, addressing a health-care inequality.

Importantly the Low MSK Disease Activity group still had a significant symptom burden, but with less evidence of active inflammation amenable to immunosuppression. These patients could potentially be offered more appropriate non-immunosuppressive therapy modalities. Our data suggests a large patient population whose needs may not be met by current research and guidelines.

SLE management guidelines have been published, covering diverse areas including diagnosis, assessment, care delivery, and therapeutics [27]. Many recommendations in these guidelines are not specific to MSK manifestations. However, for other patients with ANA-associated arthritis there are no guidelines. Further research on the described population could enhance patient outcomes in routine practice. In DEFINITION, notably, a higher proportion of non-SLE patients had ANA-associated arthritis compared with SLE patients, in terms of pure numbers.

Biomarker analysis can help determine whether a population is immunologically homogeneous and appropriate for similar therapies. The biomarker results in this study are more consistent and logical than others reported in SLE patients with arthritis. In SLE, IFN-I Scores correlate with increased skin disease activity, but not always with increased MSK disease activity—in certain studies, MSK disease activity appeared lower in IFN high patients [13, 22]. In our study, the High MSK Disease Activity cluster showed significantly higher Tetherin and IFN Score A expression.

While our study comprised a large and extensively phenotyped cohort, certain limitations persist. Notably, the sample sizes for some diagnoses were small, thereby limiting the generalizability of findings within these groups. Consequently, validation in other cohorts, along with prospective studies, are essential. Additionally, the diversity of the cohort was limited by the regional population from which it was recruited. South Asian patients were better represented in our study than many other cohorts, but other groups were underrepresented. Longer follow-up and imaging data were unavailable in our study, and future research should investigate these. The articular component of the BILAG MSK appears valid across these diagnoses, but better instruments in development, such as the LAMDA and joint counts, should be validated [28]. Finally, although we measured a wide range of gene expression and flow cytometric biomarkers, there are others emerging in autoimmunity [11].

As patient age is included as a covariate in our model, we can explore an interesting concept regarding disease stratification. Patients with an index presentation such as LN or interstitial lung disease are treated according to established guidelines. If these patients later develop a predominant MSK manifestation, it may be appropriate to categorize them within the arthritis basket. Therefore, inclusion in a basket is not static for a patient throughout their disease duration; but dependent on their predominant issue at the time of assessment.

In conclusion, these data indicate that the ANA+ arthritis basket has more unifying than dividing aspects in terms of quality-of-life impact, therapeutic usage, and biomarker variables. We describe an alternative means for classifying patients with arthritis across ANA-associated RMDs. Clinical trials in this population could generate larger effect sizes and make new guidelines and interventions available to more patients.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data underlying this article will be made available on reasonable request to the corresponding author.

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Original Article

Biologics may be **less effective** in patients who are **overweight**[1,2]

Eligible patients, weighing ≥90kg with PsA and concomitant moderate to severe PsO, may need an individualised treatment approach[4,5]

>6 in 10 adults over the age of 18 years in England are estimated to be overweight or living with obesity[3]

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Cosentyx® (secukinumab) provides **flexible dosing** based on your eligible patients' needs*[4,5]

Loading dose

Week **0**	Week **1**	Week **2**	Week **3**	Week **4**
300 mg	300 mg	300 mg	300 mg	300 mg

Maintenance dosing

Body weight **<90 kg**: 300 mg Monthly

Based on clinical response, consider up-titration
≥90 kg patients not responding to monthly maintenance dosing: 300 mg every **2 weeks**

Adapted from Cosentyx® (secukinumab) SmPC.[4,5]

*For adult patients with PsA and concomitant moderate to severe PsO, the recommended dose of Cosentyx is 300 mg with initial dosing at Weeks 0, 1, 2, 3 and 4, followed by **monthly maintenance dosing**. Based on clinical response, a maintenance dose of 300 mg **Q2W** may provide additional benefit for patients with a body weight of **90 kg or higher**.[4,5]

Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adult patients (alone or in combination with methotrexate) when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic therapy; active enthesitis-related arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[4,5]

PsA, psoriatic arthritis; PsO, plaque psoriasis; Q2W, every 2 weeks.

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NOVARTIS

UK | September 2024 | FA-11257948

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 290802 | June 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg monthly. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. 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Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity*: Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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Adverse Event Reporting:

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If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com