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Clinical science

Comparison of clinical features between patients with anti-synthetase syndrome and dermatomyositis: results from the MYONET registry

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Abstract

Objectives: To compare clinical characteristics, including the frequency of cutaneous, extramuscular manifestations and malignancy, between adults with anti-synthetase syndrome (ASyS) and DM.

Methods: Using data regarding adults from the MYONET registry, a cohort of DM patients with anti-Mi2/-TIF1γ/-NXP2/-SAE/-MDA5 autoantibodies, and a cohort of ASyS patients with anti-tRNA synthetase autoantibodies (anti-Jo1/-PL7/-PL12/-OJ/-EJ/-Zo/-KS) were identified. Patients with DM *sine* dermatitis or with discordant dual autoantibody specificities were excluded. Sub-cohorts of patients with ASyS with or without skin involvement were defined based on presence of DM-type rashes (heliotrope rash, Gottron's papules/sign, violaceous rash, shawl sign, V-sign, erythroderma, and/or periorbital rash).

Results: In total 1054 patients were included (DM, $n=405$; ASyS, $n=649$). In the ASyS cohort, 31% ($n=203$) had DM-type skin involvement (ASyS-DMskin). A higher frequency of extramuscular manifestations, including Mechanic's hands, Raynaud's phenomenon, arthritis, interstitial lung disease and cardiac involvement differentiated ASyS-DMskin from DM (all $P<0.001$), whereas higher frequency of any of four DM-type rashes—heliotrope rash ($n=248$, 61% *vs* $n=90$, 44%), violaceous rash ($n=166$, 41% *vs* $n=57$, 9%), V-sign ($n=124$, 31% *vs* $n=28$, 4%), and shawl sign ($n=133$, 33% *vs* $n=18$, 3%)—differentiated DM from ASyS-DMskin (all $P<0.005$). Cancer-associated myositis (CAM) was more frequent in DM ($n=67$, 17%) compared with ASyS ($n=21$, 3%) and ASyS-DMskin ($n=7$, 3%) cohorts (both $P<0.001$).

Conclusion: DM-type rashes are frequent in patients with ASyS; however, distinct clinical manifestations differentiate these patients from classical DM. Skin involvement in ASyS does not necessitate increased malignancy surveillance. These findings will inform future ASyS classification criteria and patient management.

Keywords: Anti-synthetase syndrome, Dermatomyositis, Cutaneous, Rashes, Skin, Malignancy, Epidemiology, MYONET, Extramuscular.

Rheumatology key messages

- Approximately one-third of patients with anti-synthetase syndrome have dermatomyositis-type cutaneous involvement.
- Certain clinical manifestations differentiate patients with anti-synthetase syndrome and dermatomyositis-type cutaneous involvement from dermatomyositis.
- Anti-synthetase syndrome with dermatomyositis-type cutaneous involvement is not associated with increased risk of malignancy.

Introduction

Antisynthetase syndrome (ASyS) is a clinical subtype of idiopathic inflammatory myopathy (IIM) characterized by the presence of disease-specific autoantibodies against aminoacyl-transfer RNA synthetase (ARS) including anti-Jo1, -PL12, -PL7, -EJ, -OJ, -KS, -Zo and -Ha. Clinical features of ASyS include mechanic's hands, Raynaud's phenomenon, interstitial lung disease (ILD), myositis, arthritis and/or fever [1–3]. Dermatomyositis (DM) is another IIM subtype distinguished by characteristic cutaneous manifestations (including Gottron's papules/sign, erythroderma, heliotrope, violaceous, periorbital, V-sign and shawl sign rashes) with or without myositis (amyopathic) and/or ILD [1]. DM-specific autoantibodies include anti-Mi2, -TIF1γ, -SAE, -MDA5 and -NXP2 [3]. Cutaneous DM-type manifestations can also be observed in ASyS patients, and therefore the current classification criteria for DM and ASyS overlap significantly, making classification of patients with anti-ARS and associated cutaneous manifestations especially challenging [4]. An international workshop from The European Neuromuscular Centre (ENMC) further highlighted this challenge, noting that ASyS is a unique and separate subgroup from DM even in the presence of DM-type cutaneous manifestations, and recommending that such patients be classified as having 'ASyS with DM-like rash' and not DM [5].

Up to 28% of patients with ASyS (defined with anti-ARS) have DM-type cutaneous manifestations [6]. However, it is not clear whether ASyS patients with DM-type cutaneous manifestations resemble patients with DM, and whether they should be regarded similarly in a clinical trial setting. Furthermore, it is not known if the presence of DM-type cutaneous manifestations confers an increased risk of DM-specific extramuscular manifestations, such as malignancy. Therefore, detailed phenotyping of a cohort of patients with ASyS with DM-type cutaneous manifestations might facilitate prediction of individual patient clinical course, clarify the need for malignancy screening, and inform future ASyS classification criteria.

We aimed to investigate the clinical manifestations in patients with ASyS and cutaneous manifestations using data from an international multicentre registry (MYONET registry, previously the EuroMyositis registry) [7].

Methods

The MYONET registry

The MYONET registry was created in 2003 [7]. The questions related to the registry were formulated following a Delphi process, and consensus discussion among Rheumatology and Neurology experts led to the creation of a uniform data collection proforma for use by all participating centres. Anonymized data from the registry were downloaded on 29 November 2021, which included 4806 cases from 112 centres, in 37 countries (Supplementary Table S1, available at *Rheumatology* online).

ASyS and DM cohort definitions

As per registry inclusion criteria, all patients with DM met Bohan and Peter 'definite' or 'probable' diagnostic criteria [8], and all patients with ASyS met diagnostic criteria proposed by Connors *et al.* [9]. For this study, cohorts of patients with ASyS or DM were defined based on the presence of ARS or DM-specific autoantibodies [3]. Patients with any of the seven ARS autoantibodies (anti-Jo1, -PL12, -PL7, -EJ, -OJ, -Zo or -KS) detectable were defined as having ASyS, and patients with any of the five DM-specific autoantibodies (anti-Mi2,

-TIF1γ, -SAE, -MDA5 or -NXP2) were defined as having DM. As Bohan and Peter diagnostic criteria for DM require cutaneous involvement, patients with DM *sine* dermatitis are not defined as DM in the registry. Five patients with both ARS and DM-specific autoantibodies were excluded. The presence of myositis-specific autoantibodies was reported by clinicians and results recorded within the registry. Methods for antibody testing varied depending on regional laboratory practices and were tabulated (Supplementary Table S2, available at *Rheumatology* online).

Case characteristics

Patient demographics including sex, age at diagnosis, smoking status, autoantibodies, and clinical characteristics were collated. Clinical characteristics including the presence of myopathic muscle weakness, seven DM-type cutaneous manifestations (heliotrope rash, Gottron's papules/sign, violaceous rash, erythroderma, periorbital rash, V-sign rash and shawl sign), 11 extramuscular manifestations (periungual erythema, calcinosis, ulceration, vasculitis, mechanic's hands, Raynaud's phenomenon, arthritis, dysphagia, alopecia, ILD and cardiac involvement), location and number of malignancies were recorded.

Definition of ASyS with and without DM-type skin involvement sub-cohorts

Sub-cohorts of patients with ASyS with DM-type skin involvement (ASyS-DMskin) and those without DM-type skin involvement (ASyS-without-DMskin) were identified based on reported case characteristics. Patients with one or more of the DM-type cutaneous manifestation were considered to have DM-type skin involvement, and those with none considered without DM-type skin involvement. The sum of reported DM-type cutaneous manifestations out of a possible seven was calculated.

Malignancy

Within the registry, malignancy is recorded including the date of diagnosis. In this analysis we considered malignancies diagnosed within 3 years of IIM onset to be 'cancer-associated myositis' (CAM). The location of CAM was compared between cohorts. Skin malignancies (including benign skin lesions such as basal cell carcinomas) were excluded except for melanoma. Malignancy was recorded variably by each centre, where in the UK the registry is linked to the National Health Service (NHS) Digital service that records malignancy, whereas other centres relied on entering malignancy data manually.

Missing data

Comparing prevalence of the clinical manifestations in our cohort with previously reported data suggested that the data were missing not at random (MNAR), and that it was more likely that data were missing when the clinical characteristic was not present. Therefore, for statistical analysis imputation of missing values was considered inappropriate, and entries of clinical characteristics that were missing were considered not present. The number of missing entries for each clinical characteristic was tabulated (Supplementary Table S3, available at *Rheumatology* online).

Statistical analysis

Between group comparisons were assessed using descriptive statistics as appropriate, with a threshold for significance set at $P < 0.05$. The Benjamini–Hochberg procedure was used to adjust for multiple comparisons to create adjusted P-values [10]. Statistical analyses were performed in R version 4.1.0 and RStudio version 1.4.1106 [11].

Ethics

All patients gave informed written consent for their data to be analysed as part of this study. The MYONET (previously EuroMyositis) registry includes multiple recruiting centres in multiple countries, where ethical approvals are required and have been sought at each centre and informed consent is obtained from all included patients. All centres obtained specific ethical approval from their local ethics committees for this study.

Results

Case characteristics

Data regarding 4806 cases were initially analysed. Patients without results of autoantibody tests available were excluded ($n = 1606$) leaving 3200 cases (Supplementary Table S4, available at *Rheumatology* online). Of these, patients without ASyS or DM-specific autoantibodies ($n = 2146$) were excluded. A cohort of 405 patients with DM-specific autoantibodies was identified, while 649 patients with ARS autoantibodies were identified (Fig. 1).

Demographics

Demographics including female sex, age at diagnosis and smoking status were compared between DM and ASyS groups. There was a significantly higher proportion of female sex in the ASyS-DMskin compared with the ASyS-without-DMskin cohorts ($n = 147/203$, 72% *vs* $n = 278/446$, 62%, $P = 0.045$). Age at diagnosis was significantly higher in the ASyS-without-DMskin cohort compared with the ASyS-DMskin cohort: 51 (interquartile range [IQR] 40–62) *vs* 47 (IQR 38–53) years, $P = 0.005$). Finally, there was a higher proportion of smokers in the ASyS cohort compared with the DM cohort ($n = 197/649$, 30% *vs* $n = 96/405$, 24%, $P = 0.023$) (Supplementary Table S5, available at *Rheumatology* online).

Prevalence of disease-specific autoantibodies

The most common autoantibody in the DM cohort was anti-Mi2 ($n = 162/405$, 40%) followed by -TIF1γ ($n = 143/405$, 35%), -MDA5 ($n = 66/405$, 16%), -SAE ($n = 39/405$, 10%), and -NXP2 ($n = 9/405$, 2%) (Supplementary Table S6, available at *Rheumatology* online). In the ASyS cohort the majority possessed anti-Jo1 ($n = 542/649$, 84%) with a lower proportion possessing other ARS: anti-PL12 ($n = 41/649$, 6%), -PL7 ($n = 35/649$, 5%), -EJ ($n = 16/649$, 3%), -OJ ($n = 10/649$, 2%) and -Zo ($n = 6/649$, 1%) (Supplementary Table S6, available at *Rheumatology* online). There were no patients with anti-Ha antibodies recorded in the registry.

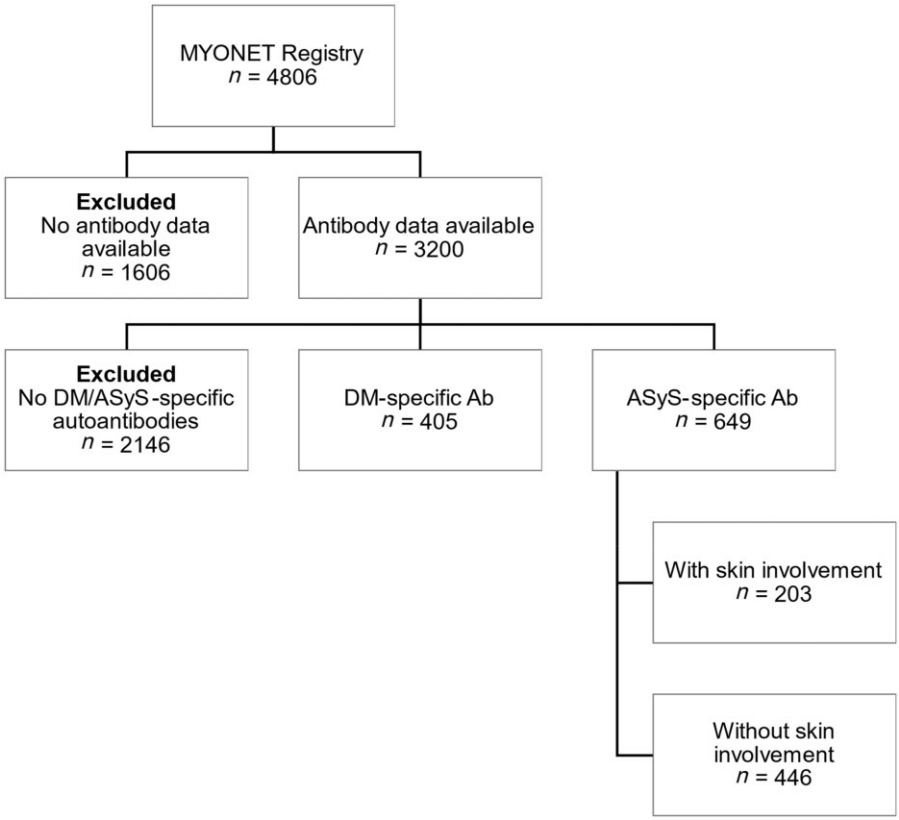

Figure 1. Flowchart illustrating the patients from the MYONET registry that were included and excluded from the study. DM-specific Ab refers to Mi2, TIF1γ, SAE, MDA5 and NXP2. ASyS-specific Ab refers to Jo1, PL12, PL7, EJ, OJ, Zo and KS. ASyS: anti-synthetase syndrome

Comparison of clinical characteristics between DM and ASyS cohorts

There were no significant differences in the presence of myopathic muscle weakness between DM and ASyS cohorts (Table 1). Patients in the DM cohort had a significantly higher frequency of each of the seven specified DM-type rashes compared with the ASyS cohort (Table 1). The extramuscular manifestations traditionally associated with ASyS (ILD, arthritis, Raynaud's, mechanic's hands) and cardiac involvement were predictably more common in this group compared with DM. Periungual erythema, ulceration, calcinosis, alopecia, vasculitis and dysphagia were more frequent in DM compared with ASyS, although there was overlap of these features across the two conditions (Table 1).

ASyS with DM-type skin involvement sub-cohort and comparison of clinical characteristics with DM cohort

The DM cohort was compared with ASyS patients possessing DM-type rashes. Of the 649 patients in the ASyS cohort, 31% ($n = 203/649$) had at least one of the seven DM-type rashes indicating skin involvement. Heliotrope rash, violaceous rash, V-sign and shawl sign were significantly more frequent in the DM cohort compared with the ASyS-DMskin sub-cohort, whereas there was no difference in frequency between DM and ASyS-DMskin for the remaining three DM-type rashes (Gottron's papules/sign, periorbital rash, erythroderma). As was observed in the overall ASyS cohort, ILD, arthritis, Raynaud's, mechanic's hands and cardiac involvement were significantly more frequent in the ASyS-DMskin sub-cohort, compared with the DM cohort. However, there were no significant differences in the frequency of myopathic muscle weakness, periungual erythema, calcinosis, vasculitis and alopecia in the ASyS-DMskin and DM cohorts. (Table 1).

For the DM cohort, the median number of DM-type rashes reported was 2 out of 7 (IQR 1–4), which was significantly higher than the overall ASyS cohort (median 0, IQR 0–1, $P < 0.001$) and comparable to the ASyS-DMskin sub-cohort (median 2, IQR 1–2, $P < 0.001$) (Supplementary Table S7, available at *Rheumatology* online).

A comparison of extramuscular manifestations between the ASyS-DMskin and ASyS-without-DMskin sub-cohorts showed that the frequency of periungual erythema, calcinosis, mechanic's hands and ulceration was significantly higher in the ASyS-DMskin sub-cohort (Table 1).

Comparison of clinical characteristics in ASyS and in DM by antibody

In patients with ASyS, DM-type cutaneous manifestations were seen in 25% ($n = 136/542$) of those with anti-Jo1, 27% ($n = 11/41$) with -PL12, 23% ($n = 8/35$) with -PL7, 19% ($n = 3/16$) with -EJ, 40% ($n = 4/10$) with -OJ and 0% ($n = 0/6$) with -Zo antibodies (Supplementary Table S8, available at *Rheumatology* online). The frequency of myopathic muscle weakness, arthritis and dysphagia within the ASyS cohort was not equally distributed across the different anti-ARS antibody subtypes where the lowest frequency of myopathic muscle weakness was seen in those with anti-PL12 antibodies (46%, $n = 19/41$), and the highest frequency of arthritis and

Table 1. Clinical manifestations of disease

	DM (n=405)	ASyS (n=649)	ASyS-DMskin (n=203)	ASyS-without-DMskin (n=446)	Adjusted P-value[a] DM vs ASyS	DM vs ASyS-DMskin	ASyS-DMskin *vs* ASyS-without-DMskin
Myopathic muscle weakness, n (%)	350 (86)	549 (85)	178 (88)	371 (83)	0.468	0.758	0.175
DM-type cutaneous manifestations, n (%)							
Heliotrope rash	248 (61)	90 (14)	90 (44)	0 (0)	<0.001	<0.001	
Gottron's papules or sign	254 (63)	141 (22)	141 (70)	0 (0)	<0.001	0.152	
Violaceous rash	166 (41)	57 (9)	57 (28)	0 (0)	<0.001	0.004	
Erythroderma	37 (9)	15 (2)	15 (7)	0 (0)	<0.001	0.599	
Periorbital rash	97 (24)	38 (6)	38 (19)	0 (0)	<0.001	0.207	
V sign rash	124 (31)	28 (4)	28 (14)	0 (0)	<0.001	<0.001	
Shawl sign	133 (33)	18 (3)	18 (9)	0 (0)	<0.001	<0.001	
Extramuscular manifestations, n (%)							
Periungual erythema	148 (37)	110 (17)	56 (28)	54 (12)	<0.001	0.0503	<0.001
Calcinosis	22 (5)	13 (2)	9 (4)	4 (1)	0.0044	0.74	<0.001
Ulceration	28 (7)	8 (1)	4 (2)	4 (1)	<0.001	0.0272	0.0221
Vasculitis	11 (3)	2 (0.3)	0 (0)	2 (0.4)	0.0018	0.0552	0.533
Mechanic's hands	45 (11)	200 (31)	84 (41)	116 (26)	<0.001	<0.001	<0.001
Raynaud's phenomenon	55 (14)	252 (39)	90 (44)	162 (36)	<0.001	<0.001	0.109
Arthritis	64 (16)	312 (48)	101 (50)	211 (47)	<0.001	<0.001	0.679
Dysphagia	134 (33)	128 (20)	47 (23)	81 (18)	<0.001	<0.001	0.254
Alopecia	47 (12)	39 (6)	18 (9)	21 (5)	0.002	0.417	0.118
Interstitial lung disease	74 (18)	441 (68)	126 (62)	315 (71)	<0.001	<0.001	0.091
Cardiac involvement	9 (2)	46 (7)	19 (9)	27 (6)	<0.001	<0.001	0.233
CAM, n (%)	67 (17)	21 (3)	7 (3)	14 (3)	<0.001	<0.001	1

[a] Chi-square test. ASyS: antisynthetase syndrome; ASyS-DMskin: antisynthetase syndrome with skin involvement; ASyS-without-DMskin: antisynthetase syndrome without skin involvement; CAM: cancer-associated myositis.

dysphagia was seen in those anti-Zo antibodies (67%, n=4/6 and 50%, n=3/6, respectively) (Supplementary Table S8, available at *Rheumatology* online). The frequency of periungual erythema, ulceration, mechanic's hands, arthritis, dysphagia, alopecia and ILD, as well as the frequency of certain DM-type cutaneous manifestations (heliotrope rash, Gottron's papules/sign, violaceous rash, periorbital rash and V-sign rash) within the DM cohort were not equally distributed across DM antibody subtypes (Supplementary Table S9, available at *Rheumatology* online). In those with anti-MDA5 antibodies, there was high frequency of extramuscular manifestations including calcinosis (13%, n=8/63), mechanic's hands (27%, n=17/63), arthritis (38%, n=24/63) and ILD (57%, n=36/63). Cutaneous manifestations were generally more frequent in those with anti-TIF1γ antibodies and in those with anti-SAE antibodies and less frequent in those with anti-MDA5 and anti-Mi2 antibodies.

Comparison of CAM in disease cohorts and by antibody

The number of patients with at least one CAM was significantly higher in the DM cohort compared with the ASyS cohort (n=67/405, 17% *vs* n=21/649, 3%, $P_{adjusted}<0.001$), and in the DM cohort compared with the ASyS-DMskin cohort (n=67/405, 17% *vs* n=7/203, 3%, $P_{adjusted}<0.001$) (Table 1). There was no significant difference between the frequency of CAM in ASyS-DMskin compared with ASyS-without-DMskin cohorts (n=7/203, 3% *vs* n=14/446, 3%, $P_{adjusted}=1$) (Table 1).

Bowel (12/405, 3% *vs* 2/649, 0.3%, $P_{adjusted}=0.013$), breast (16/405, 4% *vs* 7/649, 1%, $P_{adjusted}=0.02$), lung (10/405, 3% *vs* 3/649, 0.5%, $P_{adjusted}=0.03$) and ovarian cancers (15/405, 4% *vs* 0/649, 0%, $P_{adjusted}=0.007$) were more frequently reported in DM compared with ASyS (Supplementary Table S10, available at *Rheumatology* online). There were no significant differences in location of CAM between DM and ASyS-DMskin, or between ASyS-DMskin and ASyS-without-DMskin cohorts (Supplementary Table S10, available at *Rheumatology* online). The frequency of CAM was not equally distributed between antibody subtypes, χ^2 (degrees of freedom = 9, n=737, $P_{adjusted}<0.001$), and notably the highest frequency of CAM was observed in anti-TIF1γ patients (33%, n=46/138) (Supplementary Table S11, available at *Rheumatology* online).

Discussion

We identified several important findings including: (i) one-third of ASyS patients have DM-type cutaneous manifestations; (ii) DM-specific skin rashes in ASyS patients were associated with a distinct phenotype including higher frequency of mechanic's hands, Raynaud's phenomenon, arthritis, ILD and cardiac involvement and lower frequency of ulceration and dysphagia; and (iii) DM-specific skin rash in ASyS patients was not associated with increased risk of cancer.

First, our study demonstrates that a third of patients with ASyS have DM-type cutaneous manifestations. Our results are consistent with the previous largest published study (n=233), which found DM-type cutaneous manifestations with a prevalence of 28% in patients with ASyS [6]. This confirms that DM-type cutaneous manifestations are observed in a substantial proportion of patients with ASyS. Interestingly, our cohort also includes patients with EJ, OJ and Zo antibodies, whereas the previous study included patients with Jo1, PL12 and PL7 [6]. Our study therefore supports previous

notions that a large proportion of ASyS patients have DM-specific skin manifestations, regardless of autoantibody status. Clinicians should therefore be vigilant for DM-specific manifestations in ASyS patients and actively treat them due to their detrimental impact on quality of life [12].

Second, our study demonstrates that DM-specific rashes in ASyS patients are associated with a distinct phenotype that differentiates them from DM and from ASyS patients without DM-specific rashes. However, we also noted that increased frequency of cardiac involvement differentiated ASyS from DM, and that increased frequency of mechanic's hands, calcinosis, ulceration and periungual erythema differentiates ASyS-DMskin from ASyS-without-DMskin, suggesting that the pathogenesis underlying ASyS-specific cutaneous manifestations may have additional vascular and endothelial aetiologies over and above that which is seen in DM-specific cutaneous manifestations. We identified clinical features including increased frequency of mechanic's hands, Raynaud's phenomenon, arthritis, cardiac involvement and ILD that differentiate ASyS-DMskin from DM. Therefore, clinicians should consider a diagnosis of ASyS if these clinical signs are noted in the presence of DM-type rashes. Conversely, certain DM-type rashes (heliotrope rash, V-sign, violaceous rash and shawl sign) differentiate DM from ASyS-DMskin, and were infrequently observed in ASyS. Therefore, clinicians may not need to prioritize ASyS highly in the presence of these DM-type rashes and should instead prioritize a diagnosis of DM, and ensure malignancy screening and that other disease-specific management considerations are appropriately targeted.

Third, our study assesses whether ASyS-DMskin is associated with an increased risk of CAM and found that CAM was more frequent in DM compared with ASyS, as previously reported, but that CAM was not more frequent in ASyS-DMskin compared with ASyS-without-DMskin. The surveillance of malignancy is vital in the clinical management of DM given that it is the main cause of death in patients with IIM [14]. Interestingly, ILD and presence of anti-ARS have been associated with a lower risk of CAM, suggesting that patients with ASyS may have reduced risk of CAM compared with other IIM subtypes such as DM [1, 15]. Our findings suggest that although the cutaneous manifestations in ASyS-DMskin may be driven by similar biological processes as in DM, in ASyS-DMskin this may not confer increased risk of CAM. Therefore, in clinical practice, skin involvement in ASyS need not prompt increased surveillance or investigation for CAM.

The main strength of our study is the use of international registry data which includes the largest reported cohort of patients with DM and ASyS representing patients from centres around the world with different ethnicities. This is important given that DM and ASyS are rare diseases and would be otherwise difficult to study. However, use of registry data has limitations. First, missing data is an issue which may affect the accuracy of our findings. Second, although international collaboration is a strength when studying rare diseases, variations in clinical practice may lead to variability in reporting across centres. Third, although all patients in the MYONET registry have met current IIM classification criteria, we have further defined our DM and ASyS cohorts based on the presence of autoantibodies. However, not all patients with IIM have identifiable autoantibodies, for example, one study found 28% of DM cases were seronegative, and certain rare ASyS antibodies cannot be tested for in routine clinical practice and are therefore not represented in our study [16]. Fourth, the registry relies on clinicians with an expertise in IIM to apply IIM classification criteria prior to inclusion, and case notes were not reviewed or verified, potentially introducing a degree of misclassification. Fifth, the data analysed in this study are cross-sectional meaning clinical features that develop after entry to the registry are not captured. Finally, our analysis makes no comparison with healthy or connective tissue disease populations. Therefore, we cannot draw conclusions about whether frequency of malignancy in ASyS is higher than in the general population.

In conclusion, this is the largest study to date comparing clinical manifestations in ASyS to DM, and the first study to specifically investigate a cohort with ASyS and skin manifestations akin to DM. A third of patients with ASyS have DM-type cutaneous involvement compatible with a diagnosis of DM, but although this cohort resembles DM in terms of skin rashes, there are specific clinical manifestations which differentiate the two, and risk of CAM is lower than DM and similar to ASyS patients without DM-type skin involvement. Work to elucidate the biological processes underlying clinical manifestations in these cohorts would improve our ability to classify patients and develop targeted treatments for specific disease manifestations. These findings can inform future ASyS classification criteria and improve our ability to classify patients and develop targeted treatments for specific disease manifestations.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Data will be shared upon reasonable requests to the corresponding author.

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Protagen and Novartis Biomedical; speaker fees from Boehringer-Ingelheim, GSK and Novartis; as well as congress support from Medtalk, Pfizer, Roche, Actelion, Mepha and MSD, and a patent involving the use of mir-29 for the treatment of systemic sclerosis (US9247389, EP2331143). L.P.D. has received funding from Boehringer Ingelheim and has served on a data safety monitoring board for Corbus Pharmaceuticals. JLDB participates in Euro-NMD.

Ethics: All patients gave informed written consent for their data to be analysed as part of this study. The MYONET (previously EuroMyositis) registry includes multiple recruiting centres in multiple countries, where ethical approvals are required and have been sought at each centre and informed consent is obtained from all included patients. All centres obtained specific ethical approval from their local ethics committees for this study.

Acknowledgements

MYONET registry collaborators

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(Salford Royal Foundation Trust), Paul Sanders (Wythenshawe Hospital, Manchester), David Scott (King's College Hospital, London), David Scott (Norfolk & Norwich University Hospital, Norwich), Michael Shadforth (Staffordshire Rheumatology Centre, Stoke on Trent), Thomas Sheeran (Cannock Chase Hospital, Cannock, Staffordshire), Arul Srinivasan (Broomfield Hospital, Chelmsford), David Swinson (Wrightington Hospital), Lee-Suan Teh (Royal Blackburn Hospital, Blackburn), Michael Webley (Stoke Manderville Hospital, Aylesbury), Brian Williams (University Hospital of Wales, Cardiff) and Jonathan Winer (Queen Elizabeth Hospital, Birmingham).

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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]

Click here to visit our HCP portal and learn more

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.

References: 1. Warren RB, et al. *J Invest Dermatol* 2015;135:2632–2640; **2.** Warren RB, et al. *Br J Dermatol* 2019;180(5):1069–1076; **3.** Office for Health Improvement and Disparities. Obesity profile: short statistical commentary May 2024. Available at: https://www.gov.uk/government/statistics/update-to-the-obesity-profile-on-fingertips/obesity-profile-short-statistical-commentary-may-2024 [Accessed August 2024]; **4.** Cosentyx® (secukinumab) GB Summary of Product Characteristics; **5.** Cosentyx® (secukinumab) NI Summary of Product Characteristics.

NOVARTIS

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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.

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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

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. 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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. 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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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