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Patient global assessment and inflammatory markers in patients with idiopathic inflammatory myopathies – A longitudinal study

Karin Lodin [a,b,*], Fabricio Espinosa-Ortega [a,b], Maryam Dastmalchi [a,b], Jiri Vencovsky [c], Helena Andersson [d], Hector Chinoy [e,f,g], James B. Lilleker [g,h], Samuel Katsuyuki Shinjo [i], Britta Maurer [j], Zoltan Griger [k], Angela Ceribelli [l,q], Jiram Torres-Ruiz [m], Vazquez-Del Mercado M . [n], Dag Leonard [o], Helene Alexanderson [a,p], Ingrid E. Lundberg [a,b], for the MyoNet Registry Study Group

[a] Department of Medicine, Division of Rheumatology, Karolinska Institutet, Solna, Stockholm, Sweden
[b] Department of Gastroenterology, Dermatology and Rheumatology, Karolinska University Hospital, Stockholm, Sweden
[c] Institute of Rheumatology and Department of Rheumatology, First Medical Faculty, Charles University, Prague, Czech Republic
[d] Department of Rheumatology, Oslo University Hospital, Oslo, Norway
[e] National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, The University of Manchester, Manchester, United Kingdom
[f] Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, United Kingdom
[g] Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, The University of Manchester, Manchester, United Kingdom
[h] Manchester Centre for Clinical Neurosciences, Northern Care Alliance NHS Foundation Trust, Salford, United Kingdom
[i] Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, SP, Brazil
[j] Department of Rheumatology and Immunology, Inselspital, Bern University Hospital, University of Bern, Bern CH-3010, Switzerland
[k] Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[l] Division of Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, 20089, Rozzano, Milan, Italy
[m] Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
[n] Universidad de Guadalajara, Centro Universitario de Ciencias de la Salud, Departamento de Biología Molecular y Genómica, Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético (IIRSME), Guadalajara, Mexico
[o] Department of Medical Sciences, Section of Rheumatology, Uppsala University, Uppsala, Sweden
[p] Women's Health and Health Professional Theme, Medical Unit Occupational Therapy and Physical Therapy, Karolinska University Hospital, Stockholm, Sweden
[q] Department of Biomedical Sciences, Humanitas University, 20072, Pieve Emanuele, Milan, Italy

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ABSTRACT

Aim: To explore if patient global assessment (PGA) is associated with inflammation over time and if associations are explained by other measures of disease activity and function in patients with idiopathic inflammatory myopathies (IIM).
Methods: PGA and systemic inflammatory markers prospectively collected over five years were retrieved from the International MyoNet registry for 1200 patients with IIM. Associations between PGA, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and creatine kinase (CK) were analyzed using mixed models. Mediation analysis was used to test if the association between PGA and inflammatory markers during the first year of observation could be explained by measures of disease activity and function.
Results: PGA improved, and inflammatory markers decreased during the first year of observation. In the mixed models, high levels of inflammatory markers were associated with worse PGA in both men and women across time points during five years of observation. In men, but not in women, the association between elevated ESR, CRP and poorer PGA was explained by measures of function and disease activity. With a few exceptions, the association between improved PGA and reduced inflammatory markers was partially mediated by improvements in all measures of function and disease activity.

* Corresponding author at: Department of Gastroenterology, Dermatology and Rheumatology R92, Karolinska University Hospital, Stockholm 141 86, Sweden.
E-mail address: Karin.lodin@regionstockholm.se (K. Lodin).

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Conclusion: Increased levels of systemic inflammation are associated with poorer PGA in patients with IIM. In addition to known benefits of lowered inflammation, these findings emphasize the need to reduce systemic inflammation to improve subjective health in patients with IIM. Furthermore, the results demonstrate the importance of incorporating PGA as an outcome measure in clinical practice and clinical trials.

Introduction

Idiopathic inflammatory myopathies (IIM), known collectively as myositis, constitute a rare and heterogeneous group of diseases where a shared feature is chronic inflammation of skeletal muscle and systemic inflammation. A cornerstone in the medical treatment of IIM is to reduce inflammation to prevent muscle weakness from progressing but also to relieve skin rash, dysphagia, arthritis, improve respiratory function and reduce sickness symptoms such as fatigue and pain [1]. Conventional treatment is based on glucocorticoids, often in combination with immunosuppressive drugs. Exercise is an essential part of the treatment to improve muscle health, physical capacity and quality of life and to further reduce inflammation [2].

Reducing inflammation is of utmost importance in managing IIM [3]. However, it has not been investigated whether a reduction in inflammation is associated with improvements in the patient's subjective health. Patient global assessment (PGA) is a patient-reported outcome measure (PROM) capturing valuable information of both global health and subjective overall disease activity depending on the wording [4]. It is one of the variables in the core set measure for disease activity for myositis proposed by the "International Myositis Assessment and Clinical Studies" (IMACS) group and is frequently used in clinical practice and clinical trials. It provides important information about subjective health status beyond objectively verified health measures. PGA is often measured with a single item question "how do you rate/assess your general health status?", sometimes with the addition of a specified time reference and in relation to a specific disease. Despite the apparent simplicity, by completing the PGA the patient consolidates a surprisingly large amount of information in to a single score [5]. Subjective health ratings, and in particular self-rated health, have proven to be by far the strongest predictor of future comorbidity and death, even after adjustment for illness and objective measures in both individuals with and without disease [6–9]. The biological mechanism behind this has not been fully mapped, but many studies have shown that the brain uses inflammatory signals to assess health status [10–14].

Increased levels of inflammatory markers have been associated with poor subjective health ratings in both acute and chronic inflammatory diseases as well as in low-grade inflammatory conditions where the inflammatory markers are only slightly elevated or even within the reference values [15–19]. Thus, even a low-grade inflammatory response with inflammatory markers within the reference values can affect subjective health perception negatively [20,21]. This association between poor subjective health and inflammation has been demonstrated for several inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [22–24]. Elevation of systemic inflammatory markers is often less pronounced in patients with IIM compared to patients with other rheumatic diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus and in patients with IIM, levels of ESR or CRP often remain nearly normal even though they can be elevated in the presence of comorbidities such as cancer, interstitial lung disease or arthritis [25,26]. However, the potential importance of the level of inflammation for subjective health perception in patients with IIM is largely unknown. We hypothesized that chronic systemic inflammation in patients with IIM is associated with poor PGA and that a reduction in systemic inflammation might improve PGA. Therefore, we aimed to investigate the association between PGA and levels of systemic inflammatory markers over time in a large cohort of longitudinally followed patients with IIM. We also sought to understand whether the association could be explained by other measures of disease activity and function such as muscle strength and physical function.

Materials and methods

Dataset

MyoNet (former Euromyositis) is an international register where more than twenty participating centres worldwide prospectively have collected demographic, clinical, laboratory, serological and treatment data in a web-based registry from patients with IIM since 2003 (euromyositis.eu). In the MyoNet, visiting data including IMACS core set measures i.e. patient global assessment (PGA), physician global assessment (PhyGA), extra muscular manifestations, manual muscle test 8 (MMT-8), health assessment questionnaire (HAQ-DI) and muscle enzymes such as creatine kinase (CK), as well as inflammatory markers including CRP and ESR are routinely collected prospectively at visits regardless of disease activity. To date, more than 5000 patients have contributed to the register. A dataset consisting of 4961 patients at the time of the data export (February 1, 2021) was extracted from the registry. Nineteen centres from thirteen countries contributed with data, Table S1.

Out of 4961 patients, 1333 had information about sex and PGA. They were reclassified according to the EULAR/ACR 2017 classification criteria [27]. When information was available, cases were subclassified into "dermatomyositis" (DM), "amyopathic dermatomyositis" (ADM), "juvenile dermatomyositis" (JDM), "polymyositis" (PM) or "inclusion body myositis" (IBM). Patients with coexisting connective tissue disease who fulfilled the relevant classification criteria were reclassified as having overlap myositis and patients with DM, ADM, or PM who fulfilled the criteria for anti-synthetase syndrome (ASyS) or immune-mediated necrotizing myopathy (IMNM) were reclassified accordingly. Patients with IBM ($n = 51$) were excluded since IBM is often therapy resistant and CK is often normal. Patients with ADM ($n = 20$) were excluded from the study since they lack muscle weakness and also differ from the rest of the included patients in terms of better physical function with higher MMT-levels and lower HAQ-levels. Furthermore, ADM is a heterogenous subgroup of IIM, in which some patients may exhibit a high degree of systemic inflammation associated with rapidly progressive lung disease, and we did not want to skew our data due to this rare manifestation.

Patients with myositis which could not be classified according to the criteria ($n = 62$) were also excluded which left a total of 1200 patients at baseline, i.e., when the patient's information was first entered into the registry (Fig. S1). Longitudinal data were analyzed up to five years of follow-up from baseline where available. Information on presence of organ manifestations, such as extra-muscular variables, was retrieved from the MyoNet registry using the definitions in the registry [28]. Pharmacological treatment was given according to local practice.

Ethics

This study was approved by the Regional Ethics Committee in Stockholm (2008/1919-31/3;2009/1934-32;2013/1390-32;2017/922-32 and the National Ethics Committee: 2023-00244-02) and all patients have provided written informed consent.

Assessments

Inflammatory markers

ESR and CRP were used as markers for systemic inflammation. We

also analyzed serum levels of CK which is a marker of muscle injury and sometimes considered a surrogate marker of tissue inflammation. CK levels were calculated as ratio of upper limit of normal value. All laboratory samples were measured according to local practice.

Patient global assessment (PGA)

Patient global assessment (PGA) is one of the variables in the core set measure for disease activity for myositis as proposed by the "International Myositis Assessment and Clinical Studies" (IMACS) group. PGA, formulated by the patient, is used in clinical practice to capture both global health and subjective overall disease activity [4,29]. The versions of PGA used in this study varied slightly in concept, wording and reference period ("today" or "last week") between the countries. The wordings most commonly used were: "Considering all the ways your rheumatic disease/myositis has affected you, how do you feel your rheumatic disease/myositis is today?" or "past week?" or "How have you been feeling in general this past week, in relation to your rheumatic disease/myositis?". PGA was measured on a visual analogue scale (VAS) ranging from 0 to 100 mm where higher scores represent worse subjective health.

Measures of disease activity

Two measures were used for measuring disease activity. Extramuscular disease activity (EM) was measured by the physician on a VAS 0–100 mm where higher score represents more extra-muscular disease activity. PhyGA measures the overall disease activity of the patient at the time by the physician on a VAS 0–100 mm where higher score represent more disease activity [30].

Measures of function

Manual muscle test (MMT8) 0–80 where a higher score indicates better muscle strength, was used to assess muscle strength [31]. The self-reported Health Assessment Questionnaire Disability Index (HAQ-DI) 0–3, where lower scores indicate less disability, was used to measure functional disability [32].

Statistical analyzes

Means (standard deviation) and medians (interquartile range) were calculated from the demographic characteristics of the patients at baseline. Statistical differences between groups were tested using Student's *t*-test or Mann-Whitney *U* test for continuous data and χ^2-test for proportions.

A general linear mixed model for repeated measurements was used to characterize the relationship between PGA and inflammatory markers over the course of follow-up. In this study, we chose to include all available data points from the registry and handle missing data by choosing a mixed effect regression model. This model is suitable for analyzing registry data where data is missing at random since the model includes all values in the estimation sample [33]. The overall associations between inflammatory markers and PGA were calculated using mixed effect regression analyzes with patient identity as a random effect. The models were stratified for sex and included all available data points. The models were constructed in two steps. First, the model was adjusted for age and second, the models were adjusted for muscle strength (MMT8), disability (HAQ-DI), extra-muscular disease activity (EM) and overall disease activity according to PhyGA. The p-values were estimated by bootstrap with 2000 repetitions [34]. Age-adjusted analyzes were repeated for each of the four largest diagnostic groups to check that the association was present in all diagnostic subgroups. To investigate if changes in PGA were associated with a change in inflammatory markers, the change in PGA and inflammatory markers from baseline to 1-year follow-up was calculated and the delta values were correlated. Due to the non-normal properties of the delta values, Spearman rank correlations were used. Mediation analysis was used to test if the associations between changes in inflammatory markers and PGA were mediated by muscle strength, disability, EM disease activity or overall disease activity using the Sobel Goldman test [35]. Sobel Goldman test was chosen for the mediation analysis as a suitable method to analyze continuous independent and mediating variables and analyzing single mediators only.

STATA1 16.0 (StataCorp, LP, Texas, USA) was used for all analyzes. An α-level of 0.05 was used to test for significance.

Results

Study population at baseline

The demographic and clinical features of the 1200 patients included in the study are presented in Table 1. Most patients were women (71.9 %). Median age at diagnosis was 51.8 years for women (IQR 39.1–62.5) and 53.9 years for men (IQR 40.8–62.0). Mean time between diagnosis

Table 1
Demographic characteristics of the cohort of patients with idiopathic inflammatory myopathies from the MyoNet registry.

	Women	Men	p-value
baseline ($n = 1200$)	863	337	
1 year follow-up ($n = 736$)	537	199	
2 year follow-up ($n = 482$)	341	141	
3 year follow-up ($n = 285$)	200	85	
4 year follow-up ($n = 241$)	167	74	
5 year follow-up ($n = 191$)	135	56	
Age at first symptom (years), median (IQR)	50.5 (38.1;61.3)	52.1 (40.5;61.4)	0.210
Age at diagnosis (years), median (IQR)	51.8 (39.1;62.5)	53.9 (40.8;62.0)	0.390
Age at baseline (years), median (IQR)	56.0 (44.7;65.2)	56.6 (44.0;65.6)	0.900
Ethnicity			
Caucasian	794 (95.4 %)	311 (95.7 %)	0.690
Asian	10 (1.2 %)	4 (1.2 %)	0.120
African black	14 (1.7 %)	4 (1.2 %)	0.038*
Hispanic	14 (1.7 %)	6 (1.9 %)	0.470
Ever smoked	225 (41.1 %)	127 (56.2 %)	<0.001***
Diagnosis according to EULAR/ ACR criteria			
Polymyositis	243 (28.2 %)	98 (29.1 %)	0.750
Dermatomyositis	277 (32.1 %)	128 (38.0 %)	0.053
Overlap with a connective tissue disease	159 (18.4 %)	40 (11.9 %)	0.006**
Antisynthetase syndrome†	133 (15.4 %)	52 (15.4 %)	0.990
Immune-mediated necrotizing myopathy†	31 (3.6 %)	12 (3.6 %)	0.980
Juvenile dermatomyositis	16 (1.9 %)	5 (1.5 %)	0.660
Clinical features at baseline			
Dysphagia	331 (42.2 %)	141 (45.8 %)	
Interstitial lung disease	274 (37.9 %)	98 (34.1 %)	0.260
Heart involvement	73 (9.9 %)	39 (13.4 %)	0.100
Raynaud's phenomenon	276 (35.8 %)	62 (20.6 %)	<0.001***
Arthritis	301 (37.7 %)	74 (23.7 %)	<0.001***
Heliotrope rash	218 (31.4 %)	98 (35.8 %)	0.190
Gottron's papules	255 (36.7 %)	129 (48.1 %)	0.001***
Disease activity (VAS 0–100), mean (SD)			
Constitutional disease activity	16.1 (20.3)	13.2 (18.0)	0.053
Cutaneous disease activity	10.4 (18.6)	12.0 (19.2)	0.190
Skeletal disease activity	10.1 (16.2)	6.7 (13.6)	0.006**
Gastrointestinal disease activity	6.6 (15.1)	6.2 (14.4)	0.469
Pulmonary disease activity	10.0 (16.6)	10.3 (17.4)	0.617
Cardiac disease activity	1.1 (5.0)	1.0 (6.4)	0.051

* <0.05,.
** <0.01,.
*** <0.001.
† patients with DM, ADM, or PM who fulfilled the criteria for anti-synthetase syndrome (ASyS) or immune-mediated necrotizing myopathy (IMNM) were reclassified accordingly.

and inclusion in the registry was 4.2 years for women and 2.7 years for men. In total, 360 patients (30 %) had received a diagnosis within 3 months when entering the registry and considered as incident cases. The remaining 840 patients (70 %) were prevalent cases. Overlap with a connective tissue disorder was more common in women than in men ($p = 0.006$).

PGA at baseline was significantly higher in women (median 50, IQR 22–69) than in men (median 41, IQR 14–63), $p<0.001$, indicating a better PGA in men. Men had significantly lower ESR compared to women which was expected and is reflected in the reference values being lower in men (<15 mm/hr) compared to women <20 mm/hr). Men also had better muscle strength, lower disability, fewer extra-muscular manifestations and lower overall disease activity as measured by PhyGA, Table 2. There were no significant differences in CRP or CK levels between men and women at baseline. Women had significantly higher prevalence of arthritis and Raynaud's phenomenon compared to men at baseline whereas Gottron's papules were more common in men.

Associations between PGA and inflammatory markers over time

Median values of the inflammatory markers ESR and CRP, the surrogate inflammatory marker CK and PGA ratings over time are presented in Table 2. There was a decrease in inflammatory markers and in PGA during the first year of observation, indicating lower levels of systemic inflammation and better self-rated health 12 months after baseline. PGA ratings increased again after the second year but never reached baseline levels during the five years of follow-up.

Correlations between PGA and inflammatory markers over time are shown in Fig. 1. PGA was associated with all inflammatory markers in both women and men over time. In women, there was an association between PGA and ESR ($b = 0.31$, 95 %CI 0.21–0.40, $p<0.001$), CRP ($b = 0.22$, 95 %CI 0.12–0.32, $p<0.001$) and CK ($b = 0.86$, 95 %CI 0.65–1.08, $p<0,001$), Table 3, crude associations. Thus, for each 1 mm/h increase in ESR, PGA worsened by 0.31 points and for each 1 mg/L increase in CRP, PGA worsened by 0.22 points. In men, there was an association between PGA and ESR ($b = 0.16$, 95 %CI 0.04–0.28, $p = 0.008$), CRP ($b = 0.12$, 95 %CI 0.00–0.23, $p = 0.048$) and CK levels ($b = 0.63$, 95 %CI 0.43.0.83, $p<0.001$) over time.

In an exploratory analysis, the calculations were repeated with the 360 incident cases which had received a diagnosis within 3 months when entering the register. The associations between PGA and inflammatory markers remained significant in both women and men as expected, Table S2.

Table 2
Inflammatory markers, patient global assessment and functional measures at baseline and 1–5 years follow-up.

	timepoint (years)	women	men	p-value		timepoint (years)	women	men	p-value
PGA[1], median (IQR)	baseline	50 (22;69)	41 (14;63)	0.001***	MMT8[5], median (IQR)	baseline	68 (58;76)	74 (63;80)	<0.001***
	1	38 (15;60)	24 (6;53)	<0.001***		1	72 (61;78)	77 (67;80)	<0.001***
	2	40 (14;60)	25 (4;51)	<0.001***		2	73 (63;79)	78 (70;80)	<0.001***
	3	37 (18;61)	33 (9;60)	0.280		3	74 (69;78)	79 (66;80)	0.007**
	4	38 (12;55)	25 (4;63)	0.190		4	74 (68;79)	80 (73;80)	0.001***
	5	45 (20;65)	31 (9; 53)	0.089		5	74 (67;79)	80 (66;80)	0.017*
ESR[2], median (IQR)	baseline	16.0 (8.0;28.0)	12.0 (5.0;22.0)	<0.001***	HAQ[6], median (IQR)	baseline	0.88 (0.38;1.75)	0.50 (0;1.25)	<0.001***
	1	15.0 (8.0;24.0)	10.0 (4.0;16.0)	<0.001***		1	0.63 (0.25;1.25)	0.38 (0;.1.00)	<0.001***
	2	16.0 (8.0;26.0)	8.0 (4.0;17.0)	<0.001***		2	0.63 (0.13;1.25)	0.38 (0;.1.00)	0.001***
	3	13.5 (9.0;25.0)	11.0 (6.0;19.0)	0.053		3	0.75 (0.25;1.13)	0.56 (0;1.13)	0.160
	4	17.0 (9.0; 28.0)	12.0 (4.0;26.0)	0.025		4	0.75 (0.25;1.25)	0.50 (0;1.25)	0.074
	5	18.0 (10.0;26.0)	9.0 (5.0;18.0)	0.002**		5	0.75 (0.25;1.38)	0.75 (0;1.38)	0.410
CRP[3], median (IQR)	baseline	3.5 (1.0;7.4)	3.0 (1.0;7.0)	0.970	EM[7], median (IQR)	baseline	15 (4:30)	11 (0;26)	0.033*
	1	2.9 (1.0;6.1)	2.0 (1.0;4.5)	0.071		1	10 (0;20)	8 (0;15)	0.100
	2	2.0 (1.0;6.0)	2.0 (1.0;6.0)	0.940		2	10 (0;20)	5 (0;10)	<0.001***
	3	2.8 (1.0;6.0)	2.0 (1.0;4.0)	0.850		3	6 (0;15)	5 (0;10)	0.110
	4	2.0 (1.0;5.0)	2.0 (1.0;6.0)	0.076		4	5 (0;17)	5 (0;10)	0.410
	5	2.2 (1.0;5.0)	3.0 (1.0;5.0)	0.930		5	7 (0;18)	2 (0;10)	0.054
CK[4], median (IQR)	baseline	0.8 (0.4;3.8)	1.1 (0.5;4.5)	0.053	PhyGA[8], median (IQR)	baseline	26 (10;50)	21.5 (4;44)	0.005**
	1	0.5 (0.3;1.0)	0.7 (0.4;1.5)	0.048*		1	13 (3;29)	10 (0;20)	0.057
	2	0.5 (0.3;1.0)	0.6 (0.4;1.2)	0.990		2	10 (2;25)	6 (0;19)	0.002**
	3	0.6 (0.4;1.4)	0.8 (0.6;1.6)	0.005**		3	10 (2;20)	5 (0;15)	0.041*
	4	0.5 (0.3;1.5)	0.7 (0.4;1.4)	0.320		4	10 (0;20)	5 (0;10)	0.042*
	5	0.5 (0.3;1.2)	0.8 (0.5;1.5)	0.018*		5	10 (2;20)	5 (0;15)	0.041*

* $p<0.05$,.
** $p<0.01$,.
*** $p<0.001$.
[1] Patient Global Assessment (VAS 0–100), higher value denotes better health.
[2] Erythrocyte Sedimentation Rate (mmHg).
[3] C-Reactive Protein (mg/L).
[4] Creatine Kinase as ratio of upper limit normal.
[5] Manual Muscle Test-8 score, higher value denotes better muscle strength.
[6] HAQ-DI, Health Assessment Questionnaire-Disability index, higher value denotes higher degree of disability.
[7] Extramuscular disease activity (VAS 0–100), higher value denotes higher degree of extra-muscular disease activity.
[8] Physician Global Activity (VAS 0–100), higher values denotes higher disease activity.

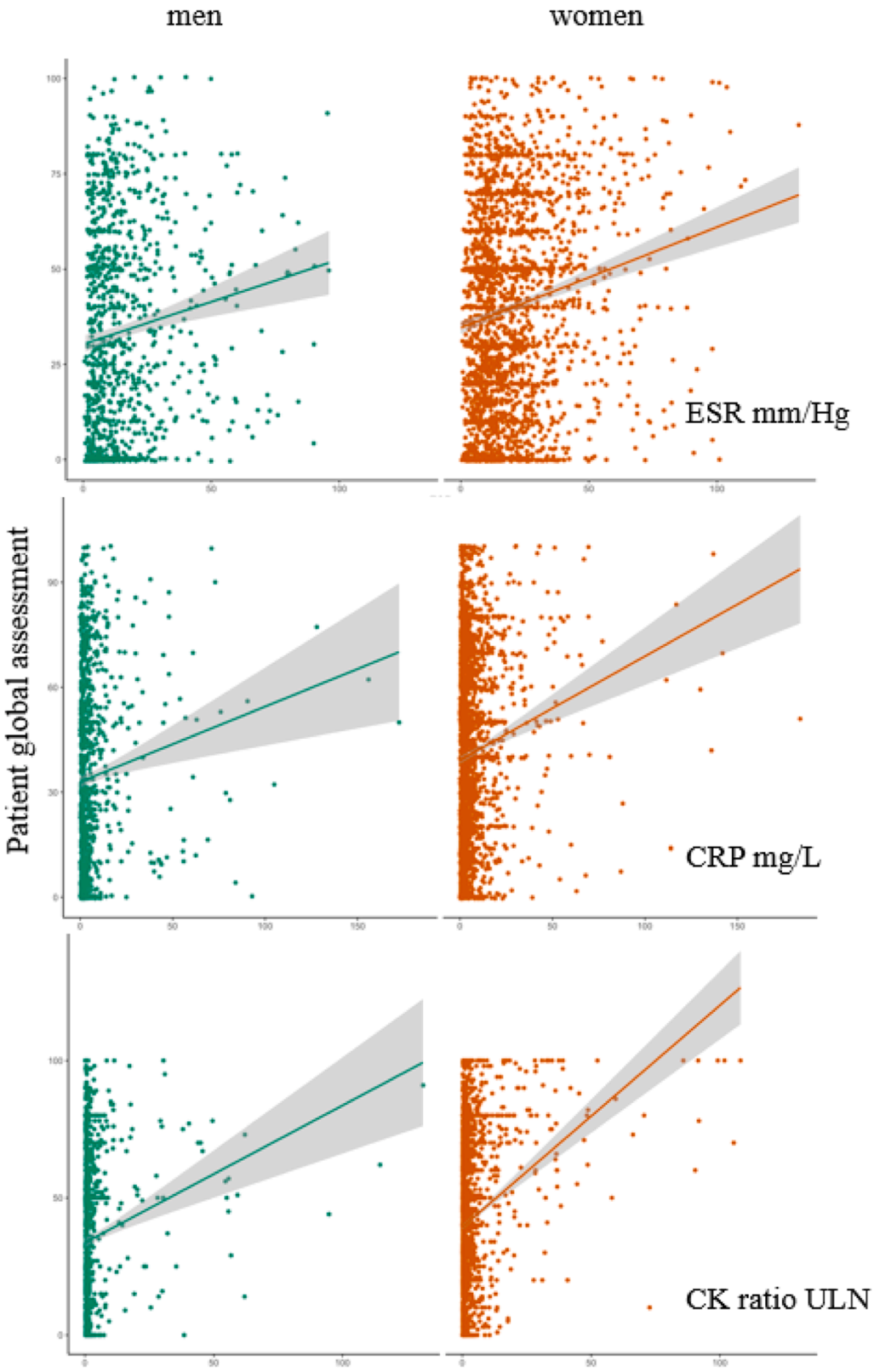


Fig. 1. Correlations between erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine kinase (CK), and patient global assessment over time. Scale x- and y-axis 0–100.

In women, the association between poorer PGA and higher levels of inflammatory markers and CK levels remained statistically significant even after adjustment for muscle strength, disability, extra-muscular disease activity and overall disease activity, Table 3. In other words, measures of disease activity and function could not explain the association between PGA and inflammatory markers in women. This was also true for the association between PGA and CK levels in men.

The association between PGA and the inflammatory markers ESR

Table 3
Longitudinal associations between PGA and inflammatory markers, adjusted for age and measures of function and disease activity.

Women	obs (n)	patients (n)	b† PGA	CI	p-value	Men	obs (n)	patients (n)	b† PGA	CI	p-value
crude model						*crude model*					
ESR[1]	2269	499	0.31	0.21;0.40	<0.001***	ESR[1]	914	220	0.16	0.04;0.28	0.008*
CRP[2]	2533	681	0.22	0.12;0.32	<0.001***	CRP[2]	989	272	0.12	0.00;0.23	0.048*
CK[3]	2639	763	0.86	0.65;1.08	<0.001***	CK[3]	985	291	0.63	0.43;0.83	<0.001***
adjusted for MMT8						*adjusted for MMT8*					
ESR[1]	1912	462	0.22	0.14;0.30	<0.001***	ESR[1]	771	202	0.10	-0.01;0.21	0.073
CRP[2]	2235	638	0.18	0.09;0.28	<0.001***	CRP[2]	860	249	0.06	-0.04;0.15	0.245
CK[3]	2427	718	0.61	0.42;0.80	<0.001***	CK[3]	894	273	0.48	0.28;0.71	<0.001***
adjusted for HAQ						*adjusted for HAQ*					
ESR[1]	2198	471	0.15	0.08;0.21	<0.001***	ESR[1]	886	211	0.05	-0.04;0.15	0.275
CRP[2]	2443	647	0.11	0.27;0.18	0.008*	CRP[2]	955	264	0.07	-0.02;.016	0.146
CK[3]	2514	703	0.41	0.26;0.57	<0.001***	CK[3]	945	278	0.36	0.10;0.62	0.006*
adjusted for extra-muscular disease activity						*adjusted for extra-muscular disease activity*					
ESR[1]	2075	476	0.17	0.08;0.24	<0.001***	ESR[1]	832	207	0.39	-0.08;0.15	0.513
CRP[2]	2314	651	0.14	0.05;0.23	0.002*	CRP[2]	897	258	0.04	-0.05;0.14	0.383
CK[3]	2466	728	0.69	0.49;0.89	<0.001***	CK[3]	917	276	0.49	0.32;0.67	<0.001***
adjusted for PhyGA						*adjusted for PhyGA*					
ESR[1]	1944	478	0.11	0.04;0.19	0.003**	ESR[1]	766	205	0.06	-0.05;0.17	0.296
CRP[2]	2329	663	0.10	0.03;0.16	0.004**	CRP[2]	895	258	0.04	-0.06;0.14	0.419
CK[3]	2530	750	0.10	0.01;0.20	0.047*	CK[3]	927	280	0.12	-0.00;0.24	0.050

[1] Erythrocyte sedimentation rate,.
[2] C-reactive protein,.
[3] Creatine kinase as ratio of upper limit normal,.
* $p<0.05$,.
** $p<0.01$,.
*** $p<0.001$.
† Fixed effect coefficients (b) and 95 % confidence intervals (CI) with bootstrapped based p-values 2000 repetitions, for the associations between PGA and inflammatory markers. All models were adjusted for age and included all available data points.

and CRP in men rendered non-significant values after adjustment for measures of disease activity and function, Table 3.

Associations between PGA and inflammatory markers in diagnostic subgroups over time

The longitudinal associations between PGA and inflammatory markers were analyzed in the four largest disease groups, Table 4. In women, higher levels of inflammatory markers were significantly associated with poorer PGA across all diagnostic IIM sub-groups except for CRP in polymyositis. In men, however, significant associations were only observed in the subgroup polymyositis.

Association between change in PGA, inflammatory markers and mediation by change in function

Changes in PGA, ESR, CRP and CK levels as tested with Spearman's correlations were most prominent between baseline and first year of follow-up, Table 5. Improvements in ESR, CRP and CK levels over the first year were weakly to moderately associated with an improved PGA.

Table 4
Longitudinal associations between PGA and inflammatory markers in diagnostic groups.

Women	obs (n)	patients (n)	b† PGA	CI	*p*-value	Men	obs (n)	patients (n)	b† PGA	CI	p-value
Dermatomyositis						Dermatomyositis					
ESR[1]	493	134	0.42	0.18;0.66	0.001***	ESR[1]	321	86	0.21	-0.01;0.43	0.063
CRP[2]	622	203	0.42	0.19;0.65	<0.001***	CRP[2]	339	99	0.10	-0.13;0.33	0.389
CK[3]	688	240	1.18	0.60;1.75	<0.001***	CK[3]	348	107	0.92	-0.53;2.37	0.212
Polymyositis						Polymyositis					
ESR[1]	654	152	0.22	0.04;0.40	0.019*	ESR[1]	246	64	0.35	0.10;0.59	0.007**
CRP[2]	720	195	0.05	-0.10;0.19	0.542	CRP[2]	259	78	0.39	0.08;0.70	0.013*
CK[3]	777	214	0.89	0.41;1.37	<0.001***	CK[3]	261	83	0.57	0.36;0.77	<0.001***
Overlap with a connective tissue disease						Overlap with a connective tissue disease					
ESR[1]	606	110	0.30	0.16;0.45	<0.001***	**ESR**[1]	155	31	0.04	-0.21;0.30	0.750
CRP[2]	594	134	0.26	0.00;0.50	0.048*	**CRP**[2]	161	37	0.23	-0.24;0.71	0.338
CK[3]	565	135	0.88	0.03;1.73	0.043*	**CK**[3]	151	37	0.41	-1.90;2.71	0.726
Antisynthetase syndrome						Antisynthetase syndrome					
ESR[1]	444	81	0.32	0.16;0.49	<0.001***	ESR[1]	167	28	-0.02	-0.25;0.21	0.838
CRP[2]	499	107	0.31	0.09;0.54	0.007**	CRP[2]	196	43	-0.02	-0.23;0.19	0.864
CK[3]	489	126	0.84	0.30;1.38	0.002**	CK[3]	185	46	0.27	-0.16;0.70	0.220

[1] Erythrocyte sedimentation rate,.
[2] C-reactive protein,.
[3] Creatine kinase as ratio of upper limit normal.
* $p<0.05$,.
** $p<0.01$,.
*** $p<0.001$.
† Fixed effect coefficients (b) and 95 % confidence intervals (CI) with bootstrapped based p-values 2000 repetitions, for the associations between PGA and inflammatory markers. All models were adjusted for age and included all available data points. Juvenile dermatomyositis and, immune-mediated necrotizing myopathy are not included in the table due to few observations.

Table 5
Spearmanś correlations for changes in PGA, ESR, CRP and CK levels between baseline and 1 year follow-up.

women	PGA	ESR	CRP	CK
PGA[1]	1.00	–	–	–
ESR[2]	0.18***	1.00	–	–
CRP[3]	0.20***	0.43***	1.00	–
CK[4]	0.27***	0.24***	0.13***	1.00
men				
PGA[1]	1.00	–	–	–
ESR[2]	0.22**	1.00	–	–
CRP[3]	0.16***	0.40***	1.0	–
CK[4]	0.28***	0.05	0.17***	1.00

[1] Patient global assessment VAS (0–100),.
[2] Erythrocyte sedimentation rate,.
[3] C-reactive protein,.
[4] Creatine kinase as ratio of upper limit normal.

To investigate if the associations between change in PGA and inflammatory markers during the first year were mediated by measures of function and disease activity, a mediation analysis was done. The association between reduced circulating inflammatory markers and improved PGA during the first year of observation was partially mediated by improvements in all measures of disease activity and function in both women and men, except for muscle strength as measured by MMT8 which did not mediate the association between PGA and inflammatory markers (Table 6). Overall, inflammatory markers were associated with measures of disease activity and function that in turn were associated with PGA. A direct association between PGA and inflammatory markers remained, however, suggesting that there are other factors besides measures of disease activity and function that link PGA and inflammatory markers in both men and women.

Discussion

In this study we found an association between PGA and systemic inflammatory markers over time in both men and women. In women, this longitudinal overall association could not be explained by measures of disease activity or function. Thus, the level of systemic inflammation was of greater importance than measures of disease activity and function when women rated their PGA. In men the association could be explained by measures of disease activity and function, indicating that these factors, rather than the inflammation itself, had a greater impact on PGA ratings in men. By and large, the association between reduced levels of inflammatory markers and improved PGA during the first year of follow-up was partially mediated by improvement in measures of disease activity and function.

Our results confirmed the hypothesis that elevated levels of systemic inflammation, although only slightly elevated compared to reference values, were associated with poor PGA. These findings corroborate previous findings of an association between systemic inflammation and subjective health ratings observed in several other conditions [15–19,22,23,36–39]. These are novel observations in patients with IIM, and a bit surprising as these patients may not have markedly elevated ESR or CRP as seen in most rheumatic or autoimmune disorders. Notably, the association between PGA and inflammation was most pronounced during the first year from time of inclusion in the registry suggesting a potential effect of the immunosuppressive treatment in the following years but this could unfortunately not be addressed due to missing information on treatment data in the registry.

We chose to include CK levels as a surrogate marker of inflammation. CK is a muscle enzyme which leaks into circulation from damaged muscle fibers. CK was often used as the only marker of disease activity in IIM but is now included as one of six items in the IMACS core-set measures of disease activity. CK levels often improve with immunosuppressive treatment suggesting CK to also be a surrogate marker of tissue inflammation [40]. CK levels depend on several factors such as sex, muscle mass and physical exercise. Furthermore, levels also vary in the different subgroups of myositis and are generally highest in patients with immune-mediated necrotizing myopathy and lowest in patients with IBM [41]. CK levels do not necessarily correlate with the severity of the symptoms in patients with IIM [40]. Here, we found a robust significant association between CK levels and PGA ratings in both women and men which remained significant even after adjusting for measures of disease activity and function. This association could be due to CK having a direct effect on subjective health appraisal or due to CK acting as a surrogate marker of inflammation and being closely linked to other inflammatory markers which in turn affect subjective health appraisal. Additional research is needed to explore the underlying mechanisms for the association between CK levels and subjective health.

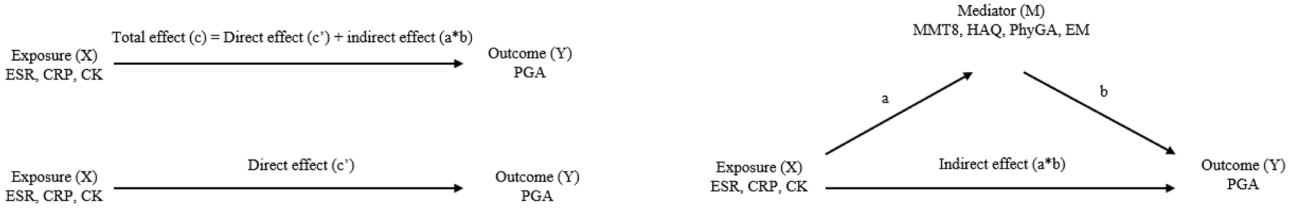
As expected from previous research in subjective health appraisal we found gender differences in the association between PGA and systemic inflammation. These findings are in line with previous reports in other diseases as well as in healthy individuals where the link between inflammation and subjective health has been somewhat more robust in women [15,16,22,42]. The findings of gender differences in subjective health appraisal have led to the suggestion that women are more inclusive in their judgments, being more perceptive and sensitive to the overall quantity of their negative feelings and minor changes in health status rather than to specific sources [22,43,44]. Poor subjective health has previously been associated with more subjective sickness symptoms such as pain and fatigue in women, and more with symptoms that are related to function and physical measures in men, which is in line with our findings [22,45]. A recent study of 50 patients with myositis reported that the main determinants of PGA was measures of physical function such as HAQ-DI (41 %), followed by measurements of fatigue, pain, physical activity, quality of life and muscle disease measures such as MMT-8 (33 %) [46]. The results were not stratified according to sex and unfortunately, inflammation was not investigated as a determinant of PGA.

We could not find any explanatory factors for the overall association between PGA and the selected inflammatory markers in women in our available data. However, we had no information about several factors that have been shown to be important determinants for subjective health appraisal. For instance, we did not have any reliable measures of pain or fatigue in this study even though both pain and fatigue have been identified by the “Outcome Measures in Rheumatology” (OMERACT) Myositis Working Group as two symptoms frequently reported and most important to be assessed by patients with myositis [47]. Further, we had no information about psychological domains including depression, psychosocial factors or body mass index and only limited information about comorbidities such as lung involvement and cancer, all of which have been shown to be important determinants of self-rated health [9,17,42,48,49].

Only a few studies have investigated determinants for PROMs in IIM. A moderate to high correlation was observed between self-rated health and muscle function as measured by MMT-8 and Functional Index-2 at 12 months follow-up in 72 Swedish patients with polymyositis and dermatomyositis [50]. Unfortunately, inflammation was not included in the correlations. On the other hand, determinants for PGA have been subject to detailed studies in patients with RA. In one cross-sectional study PGA was reported to be associated with CRP in patients with RA [24]. However, several other studies investigating the association between inflammation and subjective health in patients with RA suggest that the main determinants of PGA are pain [51–54], fatigue [52] and psychological dimensions [24] rather than inflammation. Thus, in RA, the link between inflammation and subjective health can be questioned and further research is needed to explore this area further. In our study however, we found an association between PGA and inflammatory markers in both men and women even though the association in men could be explained by other factors. The reason for the possible discrepancy between patients with IIM and patients with RA could be

Table 6
Mediation analysis for the association between PGA and inflammatory markers between baseline and 1 year.

exposure (X)	outcome (Y)	mediator (M)	a	p-value	b	p-value	c (total effect)	p-value	c'(direct effect)	p-value	a*b (indirect effect)	p-value	proportion of total effect that is mediated (%)
women													
ESR	PGA	MMT8	−0.014	0.650	−0.904	<0.001***	0.216	<0.001***	0.204	<0.001***	0.013	0.650	5.8 %
		HAQ	0.009	<0.001***	19.145	<0.001***	0.232	<0.001***	0.068	0.152	0.164	<0.001***	70.5 %
		PhyGA	0.301	<0.001***	0.738	<0.001***	0.259	<0.001***	0.036	0.439	0.222	<0.001***	85.9 %
		EM	0.183	<0.001***	0.704	<0.001***	0.241	<0.001***	0.112	0.036*	0.129	<0.001***	53.5 %
CRP		MMT8	−0.032	0.346	−1.012	<0.001***	0.279	<0.001***	0.246	<0.001***	0.033	0.347	11.8 %
		HAQ	0.007	<0.001***	19.269	<0.001***	0.239	<0.001	0.102	0.055	0.137	<0.001***	57.5 %
		PhyGA	0.335	<0.001***	0.729	<0.001***	0.298	<0.001***	0.055	0.306	0.244	<0.001***	81.7 %
		EM	0.240	<0.001***	0.625	<0.001***	0.275	<0.001***	0.125	0.036*	0.150	<0.001***	54.6 %
CK		MMT8	−0.241	<0.001***	−0.795	<0.001***	0.848	<0.001***	0.657	<0.001***	0.191	<0.001***	22.6 %
		HAQ	0.024	<0.001***	17.829	<0.001***	0.827	<0.001***	0.391	<0.001***	0.436	<0.001***	52.7 %
		PhyGA	0.971	<0.001***	0.736	<0.001***	0.771	<0.001***	0.056	0.442	0.715	<0.001***	92.7 %
		EM	0.213	<0.001***	0.577	<0.001***	0.786	<0.001***	0.663	<0.001***	0.123	<0.001***	15.6 %
men													
ESR		MMT8	−0.057	0.229	−0.976	<0.001***	0.207	0.046*	0.152	0.104	0.055	0.234	26.7 %
		HAQ	0.013	<0.001***	19.459	<0.001***	0.222	0.018*	−0.037	0.645	0.260	<0.001***	11.7 %
		PhyGA	0.208	0.015*	0.806	<0.001***	0.261	0.011*	0.093	0.231	0.168	0.016*	64.4 %
		EM	0.139	0.017*	0.776	<0.001***	0.202	0.037*	0.095	0.277	0.108	0.021*	53.2 %
CRP		MMT8	−0.072	0.128	−1.17	<0.001***	0.383	<0.001***	0.298	0.001***	0.085	0.132	22.2 %
		HAQ	0.013	<0.001***	18.856	<0.001***	0.396	<0.001***	0.150	0.076	0.247	<0.001***	62.2 %
		PhyGA	0.284	<0.001***	0.760	<0.001***	0.445	<0.001***	0.228	0.006**	0.216	0.002**	48.6 %
		EM	0.156	0.015*	0.765	<0.001***	0.363	<0.001***	0.243	0.008**	0.120	0.018*	33 %
CK		MMT8	−0.218	<0.001	−0.999	<0.001***	0.670	<0.001***	0.451	<0.001***	0.218	0.001***	32.6 %
		HAQ	0.014	0.001***	18.290	<0.001***	0.626	<0.001***	0.370	0.001***	0.256	0.001***	40.9 %
		PhyGA	0.665	<0.001***	0.794	<0.001***	0.507	<0.001***	−0.021	0.810	0.527	<0.001***	4.1 %
		EM	0.153	0.022*	0.723	<0.001***	0.504	<0.001***	0.393	<0.001***	0.111	0.025*	28.2 %



*p<0.05, **p<0.01, ***p<0.001.

due to differences in systemic and local inflammation, treatment, clinical manifestations, symptoms, psychosocial status, and several other factors. In one study patients with IIM had lower health-related quality of life compared to patients with RA suggesting that both PGA ratings as well as the determinants for PGA would likely differ between these groups of patients [55].

A major strength of this study is the large and representative sample of patients despite IIM being a rare diagnosis. The MyoNet registry is based on an international collaboration and the international multicentre cohort of 1200 IIM patients used in the present study comprise patients from 13 countries representing the entire spectrum of patients with IIM with a wide range of clinical manifestations and with data that has been prospectively collected at routine visits in the clinic, Furthermore, access to longitudinal data over five years allowed us to investigate the associations between PGA and inflammatory markers over time.

This study had some limitations. First, since we used data from an international multicentre cohort, the phrasing and time-period of PGA differed between countries. Thus, the results need to be interpreted considering the knowledge that those differences may result in a slightly varied response. Second, we lacked information about several known determinants of subjective health such as reliable information about pain, fatigue, depression, psychosocial factors, and body mass index. Third, we did not have information on immunosuppressive treatment to conduct further analyzes to investigate the effect of treatment on PGA. We also lacked information on physical activity levels or exercise which can further reduce inflammation and improve subjective health appraisal.

Conclusion

In conclusion, higher levels of systemic inflammation were associated with poorer PGA in patients with IIM. A decrease in systemic inflammation as seen after 1 year of observation was associated with an improvement in PGA. In addition to already known benefits of diminished inflammation, these findings emphasize the need to reduce systemic inflammation to improve subjective health for patients with IIM. In men, the association between inflammatory markers and PGA was explained by measures of disease activity and function. In women, none of the investigated factors explained the association suggesting that other factors may explain the association between high levels of inflammatory markers and poor PGA ratings. Further studies are needed to investigate if the association between PGA and inflammatory markers in women with IIM could be explained by inflammatory driven sickness symptoms such as pain and fatigue. In addition, the results demonstrate the importance of incorporating PGA as an outcome measure in clinical practice and clinical trials.

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Data availability

The data underlying this article were provided by the MyoNet registry (euromyositis.eu) by permission. Data will be shared on request to the corresponding author with permission of the MyoNet Registry Study Group.

Declaration of competing interest

B.M: Consultancies with Novartis, Boehringer Ingelheim, Janssen-Cilag, GSK, grant/research support from AbbVie, Protagen, Novartis Biomedical; speaker fees from Boehringer-Ingelheim, GSK, Novartis as well as congress support from Medtalk, Pfizer, Roche, Actelion, Mepha, and MSD. In addition, patent mir-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143). I.E.L: Consulting fees from Corbus Pharmaceuticals Inc and research grants from Astra Zeneca and has been serving on the advisory board for Corbus Pharmaceutical, EMD Serono. Research & Development Institute, Argenx, Octapharma, Kezaar, Orphazyme, Chugai, Bristol Myers Squibb, Galapagos, Pfizer and Janssen and has stock shares in Roche and Novartis. J.V: Consulting fees from Argenx; payment or honoraria for lectures, presentations, speakers' bureaus from Werfen and Octapharma; Participation on Advisory Board for Horizon, Boehringer, and Octapharma. H.C: Consulting fees as a speaker for GSK, UCB; Advisory Board member for Astra Zeneca, Pfizer, Argenx, Galapagos; Data and Science Monitoring Board chair for Horizon Therapeutics. The remaining authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152379.

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